BIOLOGICAL REACTIONS CAUSED BY ELECTRIC CURRENTS AND BY X-RAYS

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A theoretical study of the phenomena of excitation in the nerve by different electric currents and of the biological reactions caused by X-rays, both based upon a common principle

BY

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PREFACE

A preface is intended to give the reader a brief account of what follows. It tells something about the subjects treated and tries to explain the construction of the book. As a matter of fact, it is a part of a book which is generally neglected by the reader. In this case, however, I hope that he will pay some attention to these pages, for the fact that I am addressing myself to two groups of scientists, to wit physiologists and radiologists, who in general are not greatly interested in each other's problems, offers various difficulties in the reading of this book. Another difficulty arises from the fact that, although this is not a physical but a truly biological study, I have made an extensive use of mathematics and both groups of scientists mentioned, being biologists, are not accustomed to use a great deal of mathematics. But, as it is my wish, of course, that everyone who is interested in some of the subjects treated, should be able to read and understand them, I have tried to construct this book in such a way that the various difficulties are reduced as far as possible.

In the first part I have pointed out that the two subjects discussed, viz., the phenomena of excitation caused by electric currents and especially those of excitation of the nerve, and the biological reactions caused by X-rays are analogous to such an extent that it is highly probable that they may be explained from a common principle. In this first part, I have furthermore tried to formulate this principle and in order to apply it to the subjects mentioned, I have used the mathematical formulation. This mathematical formulation could not be avoided, for otherwise it would have been impossible to deduce the most important conclusions. However, I hope that even he who has not been trained in mathematical deduction can understand enough of the principle assumed to understand also the second or the third part. In the second part I have discussed the phenomena of local excitation of the nerve and in the third part the biological reactions caused by X-rays. Both parts are written in such a way that the reader, who is only interested in one of them, can without much difficulty omit the other one. However, to leave one part unread, will always be unfortunate, for I myself think the

most important result is that it has been possible to unite the two fields in which so many investigators have spent their energy for so many years.

In order to make things understandable for everyone I have finished both parts with a chapter called "Summary and Conclusions" in which I have left out all mathematics except the fundamental equations.

I am greatly indebted to several persons who interested themselves very much in this study and gave much good advice. In England to Dr W. H. A. RUSHTON, Cambridge, who read the provisional manuscript. His kind criticism, especially about the physiological part, was very valuable to me and made me rewrite some parts. In Sweden to Prof. Dr R. SIEVERT and Dr A. FORSSBERG, both at Stockholm; I thank Prof. SIEVERT for his good advice and encouragement to publish this study which started from one of his own numerous and splendid ideas and Dr FORSSBERG for several remarks made after having read the manuscript very carefully, especially the radiological part. And in Holland to Prof. Dr J. VAN EBBENHORST TENGBERGEN, Amsterdam, who also read the provisional manuscript and to Prof. Dr BALTH. VAN DER POL and Dr C. J. BOUWKAMP, Eindhoven, who gave useful help in solving one of the difficult mathematical problems.

Nymegen, May 1947. J. TH. V. D. W.

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Part III. Biological Reactions caused by X-and γ-Rays

LIST OF SYMBOLS USED

In this list only the principal symbols are mentioned viz. those which are of importance for the understanding of the formulae which are essentially connected with the theory. Symbols used in formulae taken from the literature are omitted.

t Time.

$\xi(t)$ Concentration at the time t of an unknown matter X responsible for the excitation of the nerve or for a biological reaction caused by Röntgen-rays.

ξ_0 Concentration of the matter X in the resting-state, before the experiment.

$x(t)$ Relative concentration at the time t of the matter X to the concentration in the state of rest.

$\varrho(t)$ Concentration at the time t of the building-blocks R from which the matter X is built up.

ϱ_0 Concentration of those building-blocks in the state of rest.

$I(t)$ General symbol of the dissimilation-coefficient at the time t.

I_0 Dissimilation-coefficient when in the state of rest.

$L(t)$ General symbol of the assimilation-coefficient at the time t.

L_0 Assimilation-coefficient when in the state of rest.

A Critical amplitude of the relative concentration of X.

τ_1 and τ_2 Relaxation-times occurring in a change of the dissimilation-coefficient and of the assimilation-coefficient respectively.

i Current-strength of a direct current or intensity of the Röntgen radiation respectively, in physical measure.

I This symbol has not always the same meaning, but acts as a simplifying substitute in the formulae with regard to various kinds of current. For direct currents I is proportional to the current strength. In the formulae concerning the biological reactions caused by X-rays I is proportional to the intensity of the radiation.

$c_1, c_2, c_3, c_4, k_1, k_2$ Proportionality constants.

T Utilization-time for electric currents passed through the nerve, or irradiation-time for Röntgen radiation.

T_H Hauptnutzzeit (H.N.Z.).

$T_{H,i}$ H.N.Z. after the nerve has been previously adapted to a "conditioning" current i.

R True Rheobase or Radiobase in "biological measure".

R_0 Theoretical Rheobase for infinitely long utilization-time.

Δ Rheobase in physical measure.

Δ_i Rheobase, in physical measure, after the nerve has been adapted to a conditioning current i.

t_c Chronaxie.

k HILL's time constant for the change in the local potential.

λ HILL's time constant for the accommodation.

$\left.\begin{array}{l}\varphi_1(t) \equiv \varphi_{n_1t}(n_1\tau_1)\\ \varphi_1(t) \equiv \varphi_{n_2t}(n_2\tau_2)\end{array}\right\}$ Poisson-functions, sigmoidally rising from 0 to 1.

PART I

GENERAL INTRODUCTION AND ESSENTIALS

I

ON ANALOGIES

Among those parts of Physiology which have been best examined, certainly belongs the part which is concerned with the phenomena that occur after electrical stimulation of the different organs, especially of the nerve.

For nearly 100 years innumerable investigators, equipped with the best expedients which time provided, have made it their life-work to examine these phenomena experimentally as well as theoretically.

Since the discovery of X-rays and the disclosure of the immense influence of these rays on living objects and the consequent possibilities for therapeutic application, another group of investigators has come, who, for almost 50 years have tried to explore this difficult territory as well, and have also discovered innumerable regularities in the phenomena.

It is very remarkable indeed, that both groups have been working completely beside each other and, as far as I know, have not seen, that between the two categories of phenomena such a parallelism exists, that it is highly probable that a common property of living matter underlies both.

I first want to illustrate this parallelism by some examples.

1a. If at two points of the nerve of a nerve-muscle preparation, an unpolarizable electrode is applied and a current is sent through the nerve for some time, then, dependent on time, strength and form of the current, a contraction of the muscle occurs. Whatever idea one may have about the origin of this contraction, one thing seems to be sure: the first cause is to be found in the displacement of the different ions present in the nerve. It is also a certain fact, that, in particular, an increase of the concentration of potassium and calcium ions at the cathode plays an important part.

1b. If a cell, a tissue, or an organ is being irradiated with Roentgen-rays, it is also certain that all subsequent phenomena are in the first instance caused by the property of X-rays of forming ions.

Polarity is absent here, of course. It has been experimentally made known that among other things, changes occur in the concentration of the K and Ca ions.

2a. If a constant current of given strength is sent through a nerve, it appears that this current should at least continue for some time in order to bring about a contraction of muscle. This minimum interval, belonging to each current strength, is called the "Utilization time" ("Nutzzeit" or "Temps utile").

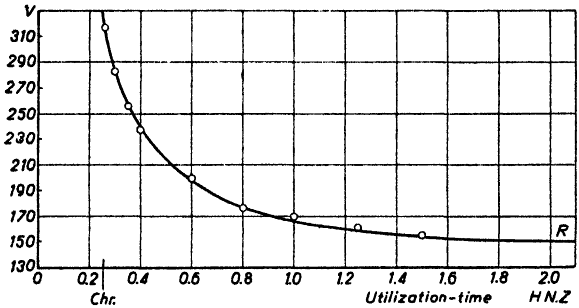


FIG. 1 – Experimental strength-duration curve for constant-current pulses. Threshold-tension V. Rheobasic tension R = 151. HILL's time-factor k = 0.402. From H. A. BLAIR, *J. gen. Physiol.*, 18 (1934).

For very short durations and high current-strengths the product

current strength · utilization time

appears to be constant.

For weaker currents this product increases in value.

Further: there is a minimum current strength, the Rheobase (LAPICQUE), below which — even after an infinitely long time — no reaction occurs. The utilization time, belonging to the Rheobase, is generally called the "Hauptnutzzeit" ("H.N.Z.", GILDEMEISTER).

Plotting the appropriate values of current strength and utilization time against each other, the well-known strength-duration diagram originates (Fig. 1).

The course of the strength-duration curve has been mathematically represented in different ways; in the simplest form by WEISZ as

$i = a + \frac{b}{t}$, after theoretical considerations by HILL as $\frac{I}{I_0} = \frac{1}{1 - e^{-\frac{t}{k}}}$, in which I_0 represents the Rheobase.

2b. With the biological reactions in response to X-rays a similar thing—differently designated—is found. In order to achieve a certain result, an appropriate dose of X-rays has to be applied. This amount is determined by the product of the intensity of the rays and the time. Here too, it appears that for shorter durations the dose is constant, for longer durations however, it has, as a rule, to be greater. For the description of this phenomenon, in Radiology called the Time-factor, contact has been made with photochemistry and it is asserted that for shorter durations the BUNSEN-ROSCOE law obtains;

$$\text{Effect} = i \cdot t,$$

while for longer durations SCHWARZSCHILD's law holds good, which has been formulated as follows:

$$\text{Effect} = i^p \cdot t \qquad (\text{generally } p < 1)$$

This law of SCHWARZSCHILD does not hold good for very long periods of irradiation, as HOLTHUSEN, for example, has shown. In case it would hold, no radiological "rheobase" would exist. If the latter *does* exist, it has not yet been experimentally ascertained. Still there have been ideas and indications which point to the existence of a radiological "rheobase". Long ago MUTCHELLER, for instance, calculated that an intensity of 0.04 r per hour would not injure the skin.

Moreover, LEA has developed a law for certain cases, the graphical representation of which shows the same sort of curve as the strength-duration curve of electrical excitation of the nerve, while I myself have deduced a law, which will come up for discussion in the course of this study.

3a. An important group of phenomena has led to the conception of "local summation" or "addition latente", by which is meant the fact, that in many cases a number of subliminal stimuli, which separately do not cause a response, *do* effect a response if they are applied shortly after each other.

The phenomenon may be reduced to the other one that one single subliminal stimulus, although it does not excite, yet causes certain changes, which also continue after the stimulus has stopped, and then, more or less exponentially disappear. KEITH LUCAS called this phenomenon the "local excitatory disturbance" and since MONNIER it is also known as "état d'excitation".

3b. We are confronted with exactly the same phenomena in Radiology. Here too, a dose of X-rays once applied appears to make itself felt long after and the possibility of gradually bringing about the desired effect by means of a great number of small daily amounts, by so-called fractionating of a large total, is generally applied in X-ray therapy. In the initial stages of the development of this therapy, suppositions were advanced that the effect of an applied dose would exponentially decrease (KINGERY, STENSTRÖM and MATTICK). The fact was overlooked that each observed effect (e.g., the erythema of the skin) is in most cases a secondary result of different possible primary effects. The conception of the "cumulative dose" as the effective sum of a number of separately applied amounts has been introduced by HOFFMANN and REINHARDT (1934), by QUIMBY and MACCOMB (1937) and by LEA (1938). Of this cumulative dose, which will be smaller than the sum total of the different applied doses, they assumed that it would decline exponentially after the last irradiation.

4a. If a condenser-discharge of extremely short duration, which is not strong enough to cause a muscle-contraction, is sent through part of a nerve, the local excitatory disturbance (l.e.d.), which results from this subliminal stimulus, can be determined by measuring the excitability at different moments after the first stimulus. So the l.e.d. is consequently determined by following up the first stimulus with new threshold-pulses.

Similar experiments have been carried out by ERLANGER and BLAIR (1931) among others. They observed that the excitability, which has appreciably increased after the first current-shock, decreases more or less exponentially towards the original value. There follows, however,—and this is very important—a second phase of diminished irritability, the post-cathodal depression, which

eventually disappears again. Hence the l.e.d. which follows after the first stimulus has a biphasic course.

4b. The irradiation with X- or γ-rays of a single cell or of a larger biological object causes disturbances which also in numerous cases have a similar biphasic course.

In A. FORSSBERG's beautiful experiments on the growth-rate of the fungus-cell *Phycomyces Blakesleeanus*, the growth-rate at first decreases after one irradiation but then rises above the normal level and finally returns to the original value.

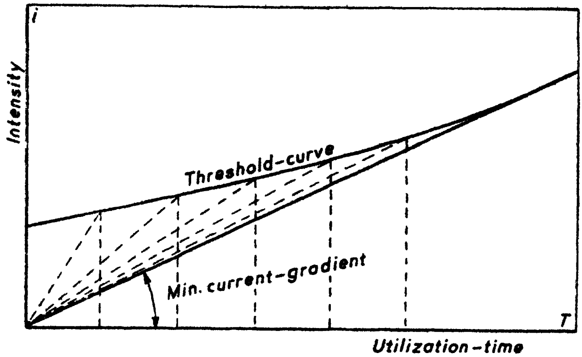


FIG. 2 – Threshold-values for linearly increasing currents with different gradients.

We see the same mainly biphasic waves, after a single irradiation of man and animals, in the numbers of the different cells of the blood, in the pH of the tissues, in the amount of certain salts in the skin etc.

5a. I further want to draw attention to an extremely important category of phenomena, the analogy of which is not too clear or rather has not been too clearly ascertained. It is concerned with the so-called accomodation.

Since DUBOIS-REYMOND, it has been known that muscle-contraction fails to occur, if the current-strength is gradually increased until it reaches a value, which, without this so-called "Einschleichen" would have caused excitation. There exists even a "minimum current-gradient". If the current-gradient is less than the minimum one, no excitation occurs, however large the final value of the current may be (Fig. 2).

5b. So far, no analogies in Radiology have been made. The reason however, is that the possibility of accomodation-phenomena with gradually increasing intensity of X-rays has never been investigated and, as I shall maintain later on, possibilities may exist here for other modes of dosing in X-ray-therapy. Every radiologist, however, who again and again perceives that tumours become X-ray-resistant, knows very well that accomodation-phenomena exist.

6. Finally, it may be useful to draw attention to one single difference.

While with excitation-phenomena durations of fractions of a second play a part, the events produced by X-rays evolve in durations which vary from minutes to several weeks. The fact has to be accounted for that the nature of the investigated effects is quite different and especially with X-rays, enormously varied. Moreover, these effects are always secondary reactions and it is quite certain that the primary effects are as quick as those with the excitation-phenomena.

II

A HYPOTHETICAL EQUATION OF METABOLISM

1. Introduction

A mathematical treatment of biological problems which rises above the physical explanation of special detailed phenomena, is confronted with two kinds of difficulties:

a. the extreme intricacy of living matter,

b. the fact that Life as a parameter of unknown nature plays a part.

This does not mean that the discovery of (statistical) laws, expressible in mathematical form, is impossible. To be sure, the living object is the most surprising and admirable ideal of organization in nature, in comparison with which the most intricate device made by man is only a poor and primitive construction. Organization, however, means order and wherever there is order there are "laws". The description in mathematical terms is only a matter of choosing symbols with which to describe and survey difficult and unsurveyable associations. Mathematics does not make problems more intricate, on the contrary it simplifies them. In the field of physics, chemistry, and astronomy, people have already recognized this for a very long time notwithstanding the fact that the properties of non-living matter are hardly less intricate than those of living matter. By careful schematization and by simple working-hypotheses a wonderful picture of nature has been developed which has given birth to so many useful applications. In biology one has generally not trodden the same path. Of course, admitting that the laws of physics and chemistry hold good even in living matter, biologists have largely taken advantage of any progress in those fields and with great success. But now and then one feels that it may be necessary to find other ways. This occurs when we replace a living object by a purely chemical or physical model and then discover that it always fails. Then we may think that this is only a consequence of the fact that the model is oversimplified, but I myself always feel that the difference between the living object and the physical model is not only a question of intricacy. However, this view is not a matter of discussion, but of conviction.

However, I am convinced that we have to try and find purely biological principles and that we should discuss them in a mathematical way in order to obtain a picture of the consequences, even if we do not know very much about the physical and chemical details which play a part. In this way, very important work has already been done by VOLTERRA, LOTKA, and RASHEWSKI—mentioning only the authors of extensive studies. Surely also, JORDAN's Quantum biology belongs to it and in the course of this study we shall meet several attempts to solve special problems like excitation of nerve and the action of X-rays in a similar way. I must mention the older work of VERWORN, who, in 1895, tried to fix ideas and to explain a series of phenomena which are related to "assimilation and dissimilation". In order to develop a common theory of the two large groups of phenomena this study deals with, I shall tackle a problem in the same field, viz., the disturbance of assimilation and dissimilation of certain substances by changes in the concentrations of ions under special circumstances. Although I shall adopt some conceptions from VERWORN's work, this does not mean that I accept the Chemical-Individual Theory. This study has nothing to do with it.

2. The organization of Life

Life is organized in unities which have the property of themselves consisting in an organization of a multitude of spatially contiguous lower unities or elements. We may perhaps assume the macromolecules, such as they are known, for instance, in the genes of cells, as the lowest biological unities. These "living molecules", to quote PFLÜGER, interacting upon each other and upon non-living molecules, form the organs of cells. In the same way the cells form the different organs of the individual and the different kinds of individuals form the people. So Life is organized at different levels. At every stage we find the same kind of organization, though the higher the level the more involved the organization. Even when we are speaking of the individuals forming a people, we must account for the fact that it is not only the men who form the people, but also the animals, the plants, the substances in the soil and the air and last but not least the geographical and political environment. All these things interact upon each other.

From this picture it follows firstly, that if it is possible to find

some valuable principle in what happens if we cause a disturbance in some biological unit, we may reduce the number of variables by considering only the next-lower elements of which the biological unit consists. Secondly, that we may apply this principle to a certain extent to biological units at every stage and thirdly, that we cannot influence one type of elements without disturbing the whole system. This last consideration made VOLTERRA and LOTKA develop their system of equations, writing the velocity by which each kind of element ξ_k changes, as a function of all other interacting kinds. So

$$\frac{d\xi_k}{dt} = f_k(\xi_1, \xi_2 \dots \xi_n, t) \qquad \begin{aligned} k &= 1, 2 \dots n \\ t &= \text{time} \end{aligned}$$

If we make some special assumptions about these functions (possibility of development in a MACLAURIN series etc.), we can deduce some conclusions about the convergence or divergence of the solutions, but it will still be generally impossible to apply the general equations to special problems, because we never know the exact functions nor even the number of them. Hence it will be necessary to reduce the number of variables once more and choose the functions in a suitable way so as to be as simple as possible, even at the risk of obtaining an over-simplified model. When we try to apply the equations to certain experiments, we shall perform these experiments in such a way that all kinds of influences are as constant as possible and only slight disturbances are to be studied.

3. A generalized conception of metabolism

From the preceding it is already clear that Life is not static but dynamic and when saying so, I do not mean that there is a physical and chemical restlessness. In the living object there is more. There is a tendency for organization, for growth, for reproduction, and even for evolution, which stops as soon as Life has disappeared. The living object acts in this way by means of a system in which all the essential parts are continuously built up and broken down, by assimilation and dissimilation, in one word—by metabolism. If one speaks about metabolism one thinks mostly of chemical processes. This is because these chemical processes are always connected with energy-transformations. A flow of new energy and matter is necessary for growth, for filling up the losses by radiation, evaporation etc. and for action and the innumerable chemical processes by which

these energy-transformations proceed are of the utmost importance. Yet I should like to range under metabolism every process whereby opposite energy-transformations are going on, even if this process is not a chemical reaction. I mean that, for instance, I also wish to call assimilation and dissimilation, the activation and inactivation of an enzyme or the formation of an ion or the neutralization of it. These processes are of equal importance to what is going on in the living object, for they precede and influence the chemical reactions. Likewise, we may also call assimilation and dissimilation the formation of new special cells and the disappearance of them. Generally speaking, whenever a certain kind of element appears, it does not matter in what way or at what stage, we shall speak of assimilation and whenever these elements disappear, it does not matter in what way or at what stage, we shall speak of dissimilation.

We see that assimilation and dissimilation are found at all stages. In order to avoid the question at what stage Life begins, we may, with VERWORN, call every substance which continuously appears and disappears a "biogenic substance".

So all kinds of cells in a tissue are biogenic substances, for they are continuously replaced by others. But also the protein molecules in each particular cell are biogenic substances, for USSING (1938) has shown by the application of deuterium compounds that within 30-120 days a complete renewal of cell-albumen results. By the application of isotopes of nitrogen and hydrogen contained in leucine, SCHÖNHEIMER, RATNER, and RITTENBERG also found that the tissue proteins were constantly being synthesized and broken down. And although the changes will be far quicker, it follows from purely physical considerations that the same obtains for enzyme-molecules which are continuously activated and inactivated, or for the molecules of a membrane which is continuously charged and discharged by surrounding ions. All are biogenic substances. We only see that the time-scale of the events diminishes as we reach a lower level. The electrical changes will be the quickest. The following chemical reactions, especially for the building up of large molecules, must be much slower, while the building up of a new cell is a process of quite another order, and so on. These metabolic processes in the sense in which I have propounded them here, are characteristic of Life. So, for instance, the difference between a living and a dead membrane lies in the fact that in the living membrane there is more

going on than the mere physical restlessness of the heat-movement and in this way we may understand why they show now and then other properties. Although all metabolic processes are closely connected with energy-transformations, we shall leave the energy-problem apart throughout this study.

4. The mathematical formulation of certain processes of metabolism

Now let $n(t)$ be the number of elements of an arbitrary biogenic substance X. Whatever be the mechanism of assimilation and dissimilation according to the general conception, we can always say that the velocity with which this number of elements changes , $\frac{dn(t)}{dt}$,is the sum of two other velocities and we can write

$$\frac{dn(t)}{dt} = -\text{ dissimilation velocity} + \text{assimilation velocity}. \qquad (1)$$

Can we obtain a more exact formulation of the right side of this equation? Of course it is generally impossible to do this in an exact way, but still we may try to construct something useful.

The first question to answer is whether the velocities of the right side are dependent on the number of elements of the considered substance X actually present or not. As for the dissimilation-velocity we may assume that it will always be so and thus, making things as simple as possible, we put

HYPOTHESIS I.

The number of elements of X, which decreases per time-unit, is proportional to the number of elements of X actually extant.

The assimilation gives more difficulties, for here we certainly have to consider two cases.

a. If one considers, for instance, the biogenic substance X to be a group of certain more or less complicated molecules which must be formed from other ones or, for instance, if the biogenic substance X is a particular group of differentiated cells, which are formed from a matrix of less-differentiated ones, then the rate of assimilation will be independent of the number of elements of X actually present. In this case, again making things as simple as possible, we may put the

assimilation-rate proportional to the number of actually present complete new or reserve building-blocks from which X has to be formed.

β. If we consider, however, a biogenic substance which multiplies itself by autosynthesis, as we often meet in biology, the rate of assimilation will be a function of the number of actually present elements of X and we may also put this rate proportional to $n(t)$. Which case are we to use in the problems we are dealing with in this study? Of course the correct answer will be that this will depend on the properties of the biogenic substance we are dealing with. However, we shall mainly consider the first case while discussing the problems mathematically. The reason is that the second possibility is especially related to growth. In the problem of nerve-excitation growth does not play any part at all, and we may assume that during the experiments which start from a steady state of the nerve, autosynthesis does not play a part either. With the biological reactions caused by X-rays (when we shall try to explain these reactions on the fungus *Phycomyces*), there is growth indeed, but this growth is linear before the experiment and also some time after the experiment, which shows that under constant conditions there is a constant flow of new matter from the environment. This seems to indicate that it is more likely that in the radiosensitive part of the cell we have a building up of substances independent of the quantity of matter of this kind actually present. However, when treating more complex reactions we shall not try to use a precise mathematical equation.

So returning to the first case we may assume

HYPOTHESIS II

The number of elements, which is being built up per time-unit, is proportional to the number of building-blocks actually present.

Hence we can write out the equation (1)

$$\frac{dn(t)}{dt} = -G(\lambda_1,t)\,n(t) + H(\lambda_2,t)\,r(t) \tag{2}$$

in which I call $G(\lambda_1,t)$ the dissimilation-coefficient, a function of all the factors which play a part in the dissimilation of X and $H(\lambda_2,t)$

the assimilation-coefficient, a function of all the parameters that affect the rebuilding of new elements from the building-blocks. Both will, in general, be intricate functions of the several, perhaps in the course of time, variable parameters and the more intricate, the higher the level of the biogenic matter X, e.g., in an arbitrary tissue they will depend on the system of alimentary bloodvessels, on the nerves, on the adjacent tissues of other kind, on the physical-chemical qualities of the tissue-liquid, on temperature, on external influences like radiation etc.

Before going on we might first replace in equation (2) the total number of elements of X, $n(t)$, by the concentration of these elements $\xi(t)$. Of course this is only allowed when there is no growth. If there is growth, the significance of the equation would even be entirely altered. For instance, in the case of a growing bacterial cell the assimilation of all essential substances is greater than the dissimilation. But if we consider the amount of substance in a very small constant volume, there will be a steady state and the concentration of these substances is constant. According to the general conception of metabolism we must say that both dissimilation- and assimilation-velocity in this small and constant volume are constant. So, if we replace the total number of elements by the concentration of these elements, we must also replace the assimilation- and dissimilation-coefficients by the appropiate ones.

The new equation will be

$$\frac{d\xi(t)}{dt} = -I(\lambda_1,t)\ \xi(t) + L(\lambda_2,t)\ \varrho(t) \tag{2a}$$

in which $\xi(t)$ means the local concentration of an actually present substance X and $\varrho(t)$ the local concentration of the building-blocks present in a certain small volume.

In this study we have to deal with changes in the ion-concentrations. It is clear that all sorts of electric charges play a part in the different chemical transformations in the colloidal milieus and we may safely postulate that most "metabolizing" substances will be disturbed more or less, if we cause a change in some special ion-concentrations. As for the influence of these special ions I assume:

HYPOTHESIS III

The rate of assimilation as well as of dissimilation may depend on the concentration of certain specific ions, on the understanding that by increasing the concentrations of these ions both processes are being stimulated and by a decrease are being retarded.

If all other parameters are kept constant, an enhancement of the concentrations of these ions will result in an enhancement of the assimilation- and also of the dissimilation-coefficient.

In order to avoid objections or misunderstanding I may add that I do not assume that an increase in every ion-concentration will necessarily enhance both dissimilation and assimilation of every directly or indirectly influenced biogenic substance. An increase of some kind of ions may, for instance, increase the dissimilation-rate of some biogenic substance X by destroying this substance. Now if the elements of this substance X are the building-blocks of another substance Y, the ions indirectly cause a decrease of the assimilation-velocity of Y. Hyp. III only tells something about those cases, where the experiments seem to indicate that the increase of some kind of ions in a primary action stimulates both assimilation and dissimilation.

As it is, each modification of these concentrations need not reveal itself immediately in its full strength. The typical configuration of the living objects with their spatially separated parts causes the modifications of the concentrations of the ions to reveal themselves only gradually in the assimilation- and dissimilation-coefficients. By slow displacements in a colloidal milieu, by many consecutive chemical processes, during which necessary affixtures of ions in definite places of large molecules become events which, within a fixed duration, will have occurred only with a certain probability, longer or shorter relaxation-times may occur. We are confronted in every department of biology with these relaxation-times as latent-, germination- or incubation-intervals. The next hypothesis I want provisionally to adopt is:

HYPOTHESIS IV

Each modification in the concentration of the ions concerned reveals itself in the assimilation- or dissimilation-coefficient after a relaxation-

time which is exclusive for each and independent of the concentrations themselves.

In this form the hypothesis can only be a rough approximation. Later on it will be substituted by a more general one which will show better that the relaxation-intervals are only mean-values. Finally it is assumed:

HYPOTHESIS V

The ultimate values of dissimilation- and assimilation-coefficients are, by a first approximation, proportional to the concentrations of the respective ions.

If a certain biogenic matter X is considered, whose concentration of the constituent elements at the time t is $\xi(t)$, while $\varrho(t)$ is the concentration of the building-blocks, with the help of these hypotheses the general equation of metabolism, in so far as it refers only to modifications in the considered ion-concentrations, is

$$\frac{d\xi(t)}{dt} = -I(t-\tau_1)\,\xi(t) + L(t-\tau_2)\,\varrho(t) \qquad (3)$$

in which $I(t)$ and $L(t)$ are consequently proportional to the concentrations of certain specific ions and τ_1 and τ_2 are relaxation times.

After all that has been said, it may be hardly necessary to repeat: firstly, that the equation of metabolism (3) may not be applied to all physiological problems and secondly, that the equation will never be more than a very elementary approximation. Whether a similar simple equation is usable for certain problems can only be decided by the fact that on applying this equation a large number of phenomena can be described. It has the same meaning as any physico-chemical model, which always has the drawback of representing things in a much too simplified a form, especially in biology.

Before starting on the application to various problems it may be useful to discuss some general properties.

III

SOME GENERAL PROPERTIES

With each experiment, care will be always taken to reduce as much as possible the different circumstances which exercise involuntary influences on the phenomena which are to be investigated. One hopes to achieve the greatest possible rest in the object, which has to be investigated. Experience has taught us that this condition does occur with biological objects, if external circumstances like temperature, humidity etc. are constant sufficiently long and care is taken that certain other conditions like careful preparation, and a suitable humoral environment are complied with. The state of rest is only external however, for numerous processes continue their work in the living object. The external rest only proves the occurrence of a steady state. What sort of influence may the preparations mentioned have on equation (3) if we intend to investigate the reactions of a certain biogenic matter X to external stimulation?

The making constant of the external circumstances may have as a result the *possibility* that I and L which certainly contain parameters of these external circumstances, become constant; while careful preparation and a suitable environment may see to it that *during* the experiment, in which I and L are modified, $\varrho(t)$ remains practically constant.

Then we can substitute ϱ_0 for $\varrho(t)$ and equation (3) can be integrated. Now it can be proved that $\xi(t)$ tends towards a certain limit, so that X reaches a steady state.

Proof. It is supposed that during the preparation

$$\lim_{t\to\infty} I(t-\tau_1) = I_0 > o$$

$$\lim_{t\to\infty} L(t-\tau_2) = L_0 > o$$

$$\text{and } \varrho(t) = \varrho_0 \text{ (constant).}$$

Let $\frac{L_0}{I_0} = c$, we may then substitute for $t > t_1$, (t_1 sufficiently large)

$$I(t-\tau_1) = I_0 + \varepsilon_1(t) > o$$

$$L(t-\tau_2) = L_0 + \varepsilon_2(t) = cI_0 + \varepsilon_2(t) > o,$$

where

$$c - \varepsilon_0 < \frac{cI_0 + \varepsilon_2(t)}{I_0 + \varepsilon_1(t)} < c + \varepsilon_0 \tag{4}$$

and for t_1 sufficiently large, ε_0 may be positive and as small as we wish. Equation (3) now becomes

$$\frac{d\xi(t)}{dt} = - \{I_0 + \varepsilon_1(t)\} \xi(t) + \{cI_0 + \varepsilon_2(t)\} \varrho_0 \tag{5}$$

If $\varepsilon_1(t)$ and $\varepsilon_2(t)$ are continuous functions for $t > t_1$ we obtain by integration

$$\xi(t) = e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} \left[\xi(t_1) + \int_{t_1}^{t} \{cI_0 + \varepsilon_2(u)\} \varrho_0 e^{\int_{t_1}^{u}\{I_0 + \varepsilon_1(v)\}dv} du \right]$$

$$e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} \left[\xi(t_1) + \varrho_0 \int_{t_1}^{t} \frac{cI_0 + \varepsilon_2(u)}{I_0 + \varepsilon_1(u)} \times \{I_0 + \varepsilon_1(u)\} e^{\int_{t_1}^{u}\{I_0 + \varepsilon_1(v)\}dv} du \right] \tag{6}$$

From (4) and (6) we obtain

$$\xi(t) < e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} \left[\xi(t_1) + \varrho_0(c + \varepsilon_0) \int_{t_1}^{t} \{I_0 + \varepsilon_1(u)\} e^{\int_{t_1}^{u}\{I_0 + \varepsilon_1(v)\}dv} du \right] \tag{7}$$

We now have

$$\int_{t_1}^{t} \{I_0 + \varepsilon_1(u)\} e^{\int_{t_1}^{u}\{I_0 + \varepsilon_1(v)\}dv} du = e^{\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} - 1 \tag{8}$$

which gives

$$\xi(t) < \xi(t_1) e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} + (c + \varepsilon_0)\varrho_0 \left\{ 1 - e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} \right\} \tag{9}$$

Likewise

$$\xi(t) > \xi(t_1) e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} + (c - \varepsilon_0)\varrho_0 \left\{ 1 - e^{-\int_{t_1}^{t}\{I_0 + \varepsilon_1(u)\}du} \right\} \tag{9a}$$

Because of $I_0 > o$ the first term on the righthand side of (9) and

(9a) becomes, with constants t_1 and t sufficiently large, as small as we wish. For constant t_1, if only t is large enough,

$$c\varrho_0 - \varepsilon < \xi(t) < c\varrho_0 + \varepsilon$$

Hence we find that

$$\lim_{t \to \infty} \xi(t) = c\varrho_0 = \xi_0 \quad \text{Q.E.D.} \tag{10}$$

Because $c = \frac{L_0}{I_0}$ from (10) it follows that

$$\frac{L_0\varrho_0}{I_0} = \xi_0 \text{ or } L_0\varrho_0 = I_0\xi_0. \tag{11}$$

In the steady state the equation (3) can thus be simplified to

$$\frac{d\xi(t)}{dt} = -I_0\xi(t) + L_0\varrho_0$$

$$\text{or } \frac{d\xi(t)}{dt} = -I_0\xi(t) + I_0\xi_0$$

and

$$\xi(t) = \xi_0 \tag{12}$$

If some agent or other is made to operate, so that I_0 and L_0 are changing both in the some sense and tending proportionally towards new values I_1 and L_1, so that again

$$\frac{L_1}{I_1} = c$$

it is clear that $\xi(t)$ again reverts to the original value ξ_0. This means that in this case, adaptation or accommodation obtains for the matter X.

In the case however, where $\frac{L_1}{I_1} = c_1 \quad (c_1 \neq c)$, a steady state will again develop, it is true, but $\xi(t)$ approaches the new value

$$\xi_1 = c_1\varrho_0 \tag{13}$$

The equilibrium between rebuilding and destruction adapts itself to another level.

Finally, let us suppose that with some experiment or other, we start from the steady state, in which the dissimilation- and assimilation-coefficients are I_0 and L_0, and ξ_0 is the resting-value. From a certain moment the experiment may cause $I(t)$ and $L(t)$ to become variable functions, on the understanding however, that they change again proportionally, so that always

$$\frac{L(t)}{I(t)} = c\left(= \frac{L_0}{I_0}\right).$$

In this case, equation (3) may be written

$$\frac{d\xi(t)}{dt} = -I(t-\tau_1)\,\xi(t) + L(t-\tau_2)\,\varrho_0 \tag{14}$$

Because

$$\frac{L(t-\tau_2)}{I(t-\tau_2)} = c = \frac{L_0}{I_0} = \frac{\xi_0}{\varrho_0},$$

we find

$$L(t-\tau_2)\,\varrho_0 = I(t-\tau_2)\,\xi_0,$$

and equation (3) becomes

$$\frac{d\xi(t)}{dt} = -I(t-\tau_1)\,\xi(t) + I(t-\tau_2)\,\xi_0 \tag{15}$$

Let $\frac{\xi(t)}{\xi_0} = x(t)$, in which $x(t)$ is the momentary relative concentration of the biogenic matter X at time t to the value at time zero, then this equation becomes

$$\frac{dx(t)}{dt} = -I(t-\tau_1)\,x(t) + I(t-\tau_2) \tag{16}$$

PART II

ELECTRICAL EXCITATION OF THE NERVE

I

INTRODUCTION, SUPPLEMENTARY HYPOTHESES AND DEFINITIONS

1. The existing theories

In the course of many years such a large number of theories on electrical excitation of the nerve have come into being, that it is impossible in this connection to discuss them completely. On the other hand, in order to form an opinion on the theory which will be worked out in this paper, it will be useful to give briefly the different points of view.

Essentially, three kinds of theories appear to exist:

a. The ion-theories
b. The tension-theories
c. The so-called mathematical theories.

a. With the ion-theories the changes in the ion-concentrations and the subsequent chemical processes are considered to be the primary cause of the reaction. Accordingly, a physical model is devised, which is to visualize what happens in the nerve-cell and from this model the mathematical formulation is derived.

The oldest ion-theory is by NERNST.

The nerve is represented as a tube, closed by two semipermeable membranes (cathode and anode) and filled with a viscous liquid in which a number of ions occur. By the current a polarization arises. The positive ions move towards the cathode and an enhanced concentration of these ions results. During this process the rate of diffusion plays an important part. The disturbance of the concentrations along the nerve, caused by the current, is opposed by the re-diffusion in consequence of the drop in concentration. The result of these two processes is the enhancement of the ion-concentrations at the cathode. Excitation will occur, if a certain critical concentration of the positive ions is reached.

The equations derived by NERNST for different types of currents have only a very restricted validity. They do not account for the existence of a Rheobase nor of accommodation-phenomena. Further-

more they are not valid for current-pulses of very short duration and all these divergences make the theory untenable.

NERNST's model has been improved by CREMER, BETHE and especially by HILL (1910). Although HILL's theory explained very well the phenomena, with the exception of the accommodation-phenomena, there were too many inexplicable difficulties, so that HILL himself dropped the theory. LAPICQUE too, the grand-master in the domain of electrical excitation-phenomena, who at first supported NERNST's theory, has virtually given up a special model.

LASAREFF's point of view is different. He does not consider the change in the concentration of all positive ions the primary cause, but assumes as the cause for the origin of a reaction-wave, a certain disturbance in the $K^{\cdot}/Ca^{\cdot\cdot}$ equilibrium. The theory starts from the well-known K-Ca antagonism. He further makes use of the fact that one group, the $K^{\cdot}$ ions, travel much faster with the current than the $Ca^{\cdot\cdot}$ ions. The excitation occurs at a certain value of the ratio $\frac{[K^{\cdot}]}{[Ca^{\cdot\cdot}]}$.

FABRE thinks that fairly slow molecular reactions follow the very rapid polarization. A certain amount of some substance has to be converted, if excitation shall occur.

For other ion-theories and particulars about them I may refer the reader to the handbooks and detailed literature.

All theories can explain a number of phenomena more or less aptly. We even get the impression that all of them contain a germ of truth.

b. With the second group of theories, the so-called tension-theories, the primary cause of excitation is considered to be found in the fact that the current causes local changes in the potential of the membrane. The displacements of the ions will be secondary events. This requires quite another physical model and the nerve is replaced by a system of resistances and capacitances, the so-called core-conductor model (fig. 3), with which, among many others, are connected the names of CREMER, SCHAEFER, EICHLER, BLAIR, and RUSHTON. But this model cannot explain all phenomena either. In particular the explanation of the accommodation-phenomena offers the greatest difficulties. On the other hand the core-conductor model has the great merit, that it has been possible to connect with it theoretical considerations about the way in which the impulse propagates itself along the nerve (RUSHTON). Yet I think it a serious objection that so

little importance is attributed to the different ions, as we know so very well that variations in the different ion-concentrations have such a great influence upon the way in which the nerve excites.

It is impossible in this study to discuss all details of these tension theories and the reader who wishes to know about them, should consult the special literature on this subject. (See, for instance KATZ: Electric Excitation of Nerve).

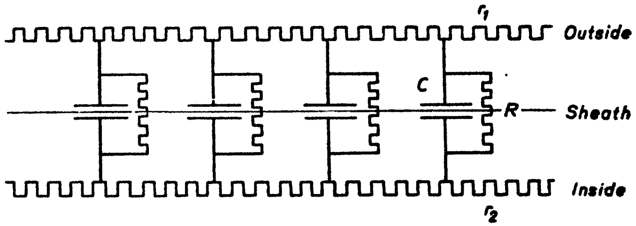


FIG. 3 – Core-conductor model. r_1, outside resistance: r_2, inside resistance: C, sheath capacity; 1/R, sheath conductivity.

c. Lastly, there are the so-called mathematical theories of RASHEVSKY, MONNIER, and HILL, which were published independently of each other in 1933, 1934, and 1936.

With these theories, which show few differences, a physical model is purposely given up, on the conviction that such a model always deviates too much from reality.

While RASHEVSKY, building on a similar theory by BLAIR, which however, corresponds less well with experiments, speaks of antagonistically acting ion-concentrations, HILL goes so far as to restrict his theory to virtual magnitudes like "local potential" and "threshold-value". By the local potential in a point of some nerve, a not further defined state is meant, which is characterized by the value V and which in the resting-state has the value V_0.

About this V is assumed: 1° that it will be altered by an electric current and that it will increase in the environment of the cathode and 2° that it will still be inclined to return to the original value V_0. The rapidity with which V changes is further specified by some hypotheses and HILL's first equation is as follows:

$$\frac{dV}{dt} = bI - \frac{(V - V_0)}{k}$$

in which I is the current-strength and b and k are constants. It is

further supposed that, if V reaches a certain threshold-value U, local excitation will occur.

In order to draw the accommodation-phenomena within the theory, HILL assumes that for a current of very short duration this value is equal to U_0. If the current continues however, the threshold-value will also rise dependent on the modifications of the local potential itself. At the same time however, the threshold-value will also incline to revert to the original value U_0. Both changes are expressed in HILL's second equation:

$$\frac{dU}{dt} = \frac{V - V_0}{\beta} - \frac{U - U_0}{\lambda}$$

In the case where Physiological Electrotonus does not play a part—and HILL only considers this case—he further assumes that the state of the fully adapted nerve is exactly as if no current is passing through it. So $\beta = \lambda$. The time-constants k and λ remain, which determine the behaviour of the nerve.

With the help of the above-mentioned hypotheses, we are now in a position to describe very well the excitation-phenomena caused by different types of current.

As has been said, the somewhat earlier theories by RASHEVSKY and MONNIER correspond essentially with the above-mentioned ones.

2. The basis of a new theory

Generally, all criticisms of the several theories can be summarized in the way KATZ did at the end of his book: "The most serious deficiency, no doubt, is the lack of any pertinent evidence as to the intimate mechanism of the "nerve membrane" and its fundamental changes. Obviously, the present core-conductor models (EBBECKE, 1933), electrical circuits (e.g., SCHMITT's ingenious model which automatically conducts and relaxes), or LILLIE's iron wire, only help to visualize the electrical properties of nerve (as, for instance, electrotonic potential spread, local and propagated action-currents) or to translate the constants of the descriptive theory into resistances and capacities, but give no indication of the physico-chemical nature of "excitation"."

Indeed it seems to me that physiologists have lost sight too much

of the fact that a nerve is neither a test-tube, filled with an aqueous solution of ions, nor a mere electric system of resistances and capacities—in other words, that the nerve is not a dead, but a very living thing indeed. That the nerve is a living object, means that with or without external or internal stimuli there is always something going on and the only essential thing about this "going-on" is, that there is an ever-lasting demolition and rebuilding, which we call metabolism. As has been said before, one should not think only in terms of chemical reactions. Metabolism may also be a continuous activation and inactivation of certain enzymes or even a continuous polarization and depolarization of a membrane. Therefore, if I shall speak in the following pages about the metabolism of a certain biogenic substance X, such a general meaning should be attached to it.

The appearance of electric phenomena, such as action-currents, cannot be considered otherwise than as signs of disturbances in these metabolic processes.

If now, we want to apply the general hypotheses of metabolism to the phenomena which occur after electrical stimulation of the nerve, it will be necessary to add a few special assumptions. Before doing so, however, I might warn the reader that these additional hypotheses partly serve only a heuristic purpose. In Chapter IV some of them will be altered and only in Chapter V (Summary and Conclusions), shall we see what is really essential and what is not.

What happens, if by means of unpolarizable electrodes a potential-difference is set up between two regularly interspaced points A and K of the nerve, so that a current flows through the nerve?

Before closing the current a steady state at every point has been created by careful preparation of the nerve. Between A and K and outside this region next to certain biogenic substances there are several ions in certain concentrations. It may be safely assumed that during the state of rest and with a not too great distance AK these concentrations are the same at any point inside and outside AK. These ions are not inactive. They take part in the assimilation nd dissimilation of certain biogenic substances. I now assume:

HYPOTHESIS VI

There is a certain biogenic substance X, the concentration of which atpoin P is a measure of the excitability at the point P.

HYPOTHESIS VII

The dissimilation-coefficient of the substance X will, in the long run, be proportional to the concentration of a certain type of cation also at the site P.

The assimilation-coefficient will, in the long run, be proportional to the concentration of another type of cation similarly at P.

As the number of elements of X in the neighbourhood of the site P is determined by the concentration of X at P and the number of elements of the extant reserves round P is similarly determined by the concentration of these elements at P, the equation of metabolism during the state of rest becomes (12)

$$\frac{d\xi(t)}{dt} = - I_0\xi(t) + L_0\varrho_0 \ , \ \xi(t) = \xi_0$$

in which ξ_0 is consequently the concentration of the biogenic matter X, ϱ_0 the concentration of the reserves, while I_0 is proportional to the concentration of one type and L_0 proportional to the concentration of the other type of cation.

In the state of rest, before the experiment, all these magnitudes are constants for every part of the nerve.

3. The origin of the Physical Electrotonus

If, however, a current is sent through AK, a displacement of the cations along the whole nerve will occur. At K, the concentration of both ions increases and at A it decreases. The consequence of these displacements and of a possible polarization of the anions is the origin of the so-called *Physical Electrotonus.*

The exact disposition of the concentrations of the cations along the nerve through the applied potential-difference and the current thus originated, depends on so many unknown factors which refer to the structure of nerve, that I wish to leave this undecided.

In a surely over-simplified way we may look upon this displacement as in a manner resembling NERNST's model (Fig. 4), but it seems to be more probable that the displacements of the ions only take place in the immediate surroundings of the membrane, for experimentally it has appeared 1°. that the greater part of the

current flows along the outside of the nerve and 2^0. that in the very short times in which the reactions take place, the ions are only submitted to very small displacements. Still the fact that outside and inside the nerve a potential-drop will originate, will at any rate cause changes in the ion-concentrations, especially in the neighbourhood of anode and cathode. I assume:

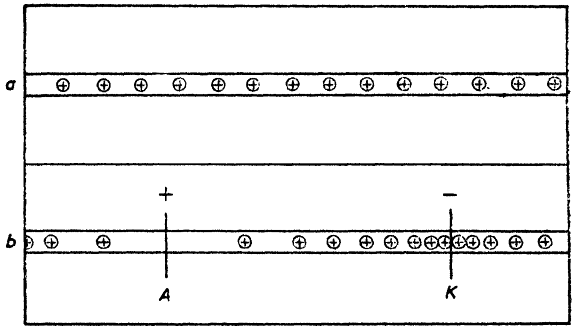


FIG. 4 – Scheme of the displacement of cations by a polarizing current. a, before closing the current; b, after closing.

HYPOTHESIS VIII

At the cathode the ultimate increase of the different cations is, by a first approximation, proportional to the resting-concentration and to the current-strength.

At the anode the concentrations of the cations will gradually decrease to zero when the current-strength increases.

Hence we have for the cathode

$$\left.\begin{aligned} I(t) &= I_0(1 + c_1 i) \\ L(t) &= L_0(1 + c_2 i) \end{aligned}\right\} \quad (17)$$

For the anode

$$\left.\begin{aligned} I(t) &= \frac{I_0}{1 + c_3 i} \\ \text{and } L(t) &= \frac{L_0}{1 + c_4 i} \text{ approximately.} \end{aligned}\right\} \quad (18)$$

For points between the anode and cathode and outside these

regions too, analogous relations hold good. For points far from A and K, I and L maintain their resting-values I_0 and L_0.

The changes of I and L, at the different points of the nerve, cause the metabolizing-process underneath the cathode to be appreciably quickened and here most considerably, whereas at the anode the process is most strongly retarded.

What we know about the displacement of the different cations, and what conclusions we may consequently draw, which point in the direction of the theory here proposed, can best be said by quoting what SCHAEFER writes on this subject:

"Hier bestand die Aussicht, die Reizvorgänge mit der Stauung bestimmter, spezifischer Ionen in Beziehung zu setzen, und während BETHE die Säuerung für wesentlich ansah, hat sich heute das Schwergewicht der Betrachtung den Kaliumionen zugewandt. Kaliumionen lockeren auf, wie wir mehrfach sahen; sie wirken quellend, so wie die Ca-ionen entquellend und dadurch abdichtend wirken. Diese Effekte sind auch mikroskopisch sichtbar; sie zeigen den allgemeinen Synergismus zwischen Kathode und Kalium einerseits, zwischen Anode und Kalzium anderseits, ein Synergismus, der seit der Zeit LOEB's die Physiologie stark beherrscht und eine Zeit lang die Erklärung aller Reizvorgänge abgegeben hat. Ich will nicht behaupten, dass wir die alten Anschauungen LOEB's wieder aufgenommen hätten, der glaubte dass die Erregung auftrete, wenn das Gleichgewicht in der Relativkonzentration zweier Ionen (z.B.K/Ca) um einen bestimmten Betrag gestört sei. Doch müssen wir ja irgendwelche spezifischen Ionenwirkungen annehmen, die uns die Membraneffekte von K und Ca verständlich machen. So hat man nachzuweisen versucht, dass bei der Durchströmung des Nerven die K-Ionen sich tatsächlich an der Kathode anreichern, an der Anode aber vermindern. Der Effekt ist erklärlich, denn die an K sehr reiche Innenleiterstrombahn wird ihre Kationen ja in der Tat gegen die Kathode wandern lassen. So wäre eine kathodische Auflockerung vielleicht nur ein K-Effekt und der Synergismus Kalium-Kathode wäre tatsächlich eine Identität. Das mag dann auch die berühmten Färbebilder BETHE's erklären. Durchströmt man nämlich einen Nerven längere Zeit mit Gleichstrom, fixiert ihn und färbt ihn dann, z.B. mit Toluidinblau, so zeigt die Anode keine, die Kathode starke Färbung. Dieser einfache Versuch hat der Erklärung relativ viele Schwierigkeiten bereitet. BEHTE nahm ursprünglich an, dass die

färbbare "Fibrillensäure" an der Anode durch Alkaliabscheidung neutralisiert, an der Kathode aber verstärkt werde; es ist also seine reiztheoretische Anschauung, dass Säuerung und Alkalisierung die Effekte des Stromes bestimmen. Später hat man die Kathodenfärbung als Wirkung der Membranlockerung aufgefasst, die Wirkung an der Anode entsprechend als Verdichtung, doch auch diese Ansicht kann nicht allein zur Erklärung ausreichen, denn es lässt sich leicht auch eine dichtere Färbung der Anode, eine schwache der Kathode feststellen. Der alte Versuch BETHE's ist nämlich in seinem Zustandekommen an dem engen Bereich von p_H 5,6–5,9 gebunden und eine plausible Erklärung des widersprechenden Verhaltens ist nur auf einer ganz neuen Basis möglich. So hat sich herausgestellt, dass Farbstoffe mit hohem Redoxpotential die Färbung besonders gut hervortreten lassen und eine gangbare Erklärung ist dann die, dass die Kathode das Redoxpotential des Nerven erhöht, die Anode es senkt, so dass an der Anode eine Entfärbung des Farbstoffes zustandekommt. Also ist die differentielle Färbbarkeit ein Abbild chemischer Affinitätsumwandlungen, ein Ergebnis, das etwas überraschend ist, das uns zugleich einen Hinweis darauf gibt, dass unter Anoden und Kathoden auch ganz verschiedene Oxydo-Reduktionsgleichgewichte herrschen müssen. Dass am Ort der Reizung, also der Durchströmung, ein erhöhter Sauerstoffverbrauch, ein sogenannter "Reizungsstoffwechsel" stattfindet, ist von WINTERSTEIN schon nachgewiesen worden. Allerdings fehlt uns noch die Möglichkeit, diesen chemischen Vorgängen in Membranen und Axonen einen sinnvollen Platz anzuweisen und sie in ein System der Reizwirkungen des Stromes einzubauen."

4. The Physiological Electrotonus

Besides the *Physical Electrotonus* we distinguish the *Physiological Electrotonus*, introduced by PFLÜGER. By the latter is meant that a continuous current, which is sent through part AK of a nerve and which is not strong enough to cause a contraction of muscle, causes interpolar and extrapolar changes, which appear in a difference of excitability at the different sites of the nerve.

The Physiological Electrotonus depends not only on the strength of the current (Fig. 5), but also on other factors. EICHLER (1915 showed that, at a low temperature (5^0 C), the electrotonic changes

are negligible. SOLANDT (1936) finds the same too. CHWEITZER (1935) and BOUMAN (1936) proved that an increase of K-concentration around the nerve alters the Electrotonus and, in the case of a strong concentration, even reverses it. With most experiments and in all theories these changes are consequently considered secondary and the circumstances are often chosen in such a way that they may be neglected.

Since it has appeared that these phenomena too may be arranged

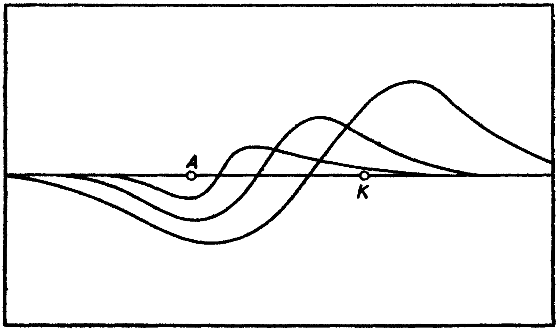


FIG. 5 – PFLÜGER's scheme. Electrotonic changes of excitability in the different points of a nerve, caused by polarising currents of various strength.

under the new theory, I define as the *Tonus* of the matter in the resting state X, the ratio $\frac{L_0}{I_0} = C$ viz., the relation of the concentrations of the assimilating and dissimilating ions.

If for a longer time a constant current flows through part of the nerve, in the same manner I define as the *Physiological Electrotonus* at a point P of the nerve, the ratio $\frac{L(t)}{I(t)}$. So, at the cathode, the Physiological Electrotonus becomes

$$\frac{L(t)}{I(t)} = \frac{L_0(1 + c_2 i)}{I_0(1 + c_1 i)} = C_i \tag{20}$$

and at the anode

$$\frac{L'(t)}{I'(t)} = \frac{L_0(1 + c_3 i)}{I_0(1 + c_4 i)} = C_i' \tag{21}$$

The fact that under suitable circumstances the electrotonic phe-

nomena are absent means, that for each point of the nerve, even during the passing of the current

$$C_i = C_i' = C,$$

which means that $c_1 = c_2$ and $c_3 = c_4$.

5. The condition for excitation

As a last hypothesis I want to propose

HYPOTHESIS IX

If at an arbitrary point P the concentration of the biogenic matter X has reached a certain critical value, the stable relations in the nerve will become unstable and from P a reaction-wave will originate, which will be propagated along the nerve and cause a muscle contraction.

6. The two possibilities: $\tau_1 > \tau_2$ and $\tau_1 < \tau_2$

By advancing the above-mentioned hypotheses all conditions have been created to treat the different phenomena of electrical excitation mathematically.

A peculiar difficulty however, presents itself. As regards the relaxation-times τ_1 and τ_2 two cases may be distinguished:

$$\tau_1 > \tau_2 \text{ and } \tau_1 < \tau_2.$$

The significance of this is, that in the first case, at a change in the ion-concentrations, the rate of assimilation of X changes before the rate of dissimilation, whereas in the second case exactly the opposite occurs. Experimentally it cannot be ascertained which case is to be preferred, but theoretically all phenomena can be explained with equal precision by both assumptions.

It is unfortunate however, that the mathematical treatment of both cases produces other formulae and it is therefore necessary to treat both cases separately.

II

THE CASE $\tau_1 > \tau_2$

The fact that $\tau_1 > \tau_2$ has, in view of the equation of metabolism, the following significance:

Before the experiment the biogenic matter X, which is, after all, responsible for the creation of a muscle-contraction, has the same concentration in all parts of the nerve. If for a short time a current passes through the nerve, apparently nothing happens during the time τ_2: the concentration remains ξ_0.

Since with the help of the cathode-ray oscillograph we are in a position to measure the "something which happens" by the occurrence of so-called action-currents, it has become possible to ascertain this relaxation-time. For the much used sciatic nerve of the frog it has a value varying from 0.16 to 0.41 σ (ERLANGER and BLAIR). SCHAEFER supposes that the polarization-phenomena develop during this time. So, τ_2 sec. after the closing of the current, the rate of assimilation at the cathode is increased and decreased at the anode, dependent on the current-strength. This period lasts just as long as the current flows; immediately after, according to the equations, the rate of assimilation will revert to its original value. The rate of dissimilation shows similar changes, only beginning after the time τ_1. So the changes in the rate of dissimilation have a time-lag behind those in the rate of assimilation. The result of these various changes is a continuous change of the concentration of X and it may be that the critical concentration of X, at which the stable condition changes into an unstable one and a reaction-wave will travel towards the muscle, is reached.

If the current is too weak, the critical concentration will not be reached. In this case we speak of a subliminal or sub-threshold current. The minimum current-strength which occasions the reaching of the critical concentration is the Rheobase and the time during which this current flows is the so-called "Hauptnutzzeit". This H.N.Z. is equal to $\tau_1-\tau_2$ and amounts to about 3 σ for the sciatic nerve of the frog. The supposition that the dissimilation has a time-lag behind the assimilation is rather attractive. It is known that K and $Ca^{\cdot\cdot}$ ions play a very important part, while it is also known that

the $K^{\cdot}$ ion releases in the nerve acetylcholine, which, if injected in a very small amount, immediately effects a muscle-contraction. We are consequently inclined to suppose that the biogenic matter X was nothing but acetylcholine, which with the help of ($K^{\cdot}$) ions would be assimilated and perhaps dissimilated with the help of ($Ca^{\cdot\cdot}$) ions. I want expressly to point out however, that this supposition is not essential; it only serves to make things clearer. The increase of the concentration of X may also be compared with the rise of the "local potential" according to HILL.

The consequence of the existence of the relaxation-times is, that the elaboration of the general equation of metabolism disintegrates into a number of separate differential-equations, each of which describes part of the course of $\xi(t)$ in the form of an analytical function. With the elaboration of the different types of current, the magnitude of τ_2 appears to have hardly any influence on the formulae. Since τ_2 is also small as regards τ_1, I shall provisionally put $\tau_2 = o$ and afterwards examine the consequences of this simplification. Now we can write τ instead of τ_2.

Further I shall treat at first the case that no electrotonic complications will occur. That will be if $c_1 = c_2$ and $c_3 = c_4$. This again has as a result that the general equation (3) may be substituted by the equation (See page 21).

$$\frac{dx(t)}{dt} = -I(t-\tau)\,x(t) + I(t) \tag{16}$$

in which $x(t) = \frac{\xi(t)}{\xi_0}$, the relative concentration of X with regard to the resting-concentration. In the state of rest $x(o) = 1$. Let the critical relative concentration be $1 + A$. Hence A is the critical amplitude.

a. Electrotonic complications will not occur ($c_1 = c_2$; $c_3 = c_4$)

1. Constant current of short duration which causes no excitation

In this case we may write at the cathode: $I(t) = I_0(1 + ci) = I_0(1 + I)$, writing, I for ci, in which consequently I is proportional to the current-strength. It might be said: I is the current-strength

in biological measure. The constant c however, is not characteristic for the nerve. It certainly depends on the distance of the electrodes, on temperature, environment, and the way in which the nerve has been prepared. Furthermore, it is not equal at all points near the cathode.

The general equation disintegrates into the following equations:

$$\left.\begin{aligned}
\frac{dx_1(t)}{dt} &= -I_0 x_1(t) + I_0(1+I) & o < t < T \\
\frac{dx_2(t)}{dt} &= -I_0 x_2(t) + I_0 & T < t < \tau \\
\frac{dx_3(t)}{dt} &= -I_0(1+I)x_3(t) + I_0 & \tau < t < \tau + T \\
\frac{dx_4(t)}{dt} &= -I_0 x_4(t) + I_0 & \tau + T < t
\end{aligned}\right\} \quad (22)$$

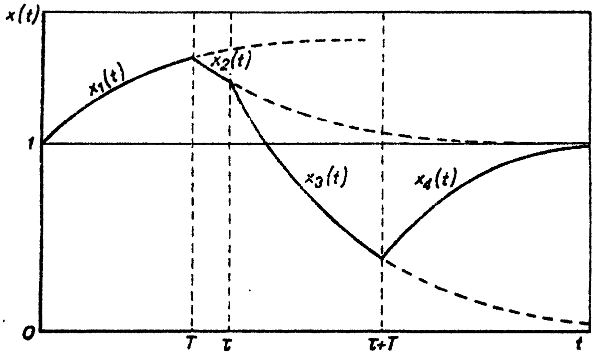


FIG. 6 – Course of the Rel. Conc. of X at the cathode with a constant current of finite duration T ($\tau_2 = 0$).

in which

$$\left.\begin{aligned}
x_1(o) &= 1 \\
x_1(T) &= x_2(T) \\
x_2(\tau) &= x_3(\tau) \\
\text{and } x_3(\tau+T) &= x_4(\tau+T)
\end{aligned}\right\} \quad (23)$$

The solutions of these simple equations determine the course of

the relative concentration of X, as represented in Fig. 6. It is a diphasic wave, composed of 4 different functions, respectively:

$$\left.\begin{array}{ll} x_1(t) = 1 + I(1-e^{-I_0 t}) & o < t < T \\ x_2(t) = x_1(T)e^{-I_0(t-T)} + 1 - e^{-I_0(t-T)} & T < t < \tau \\ x_3(t) = x_2(\tau)e^{-I_0(1+I)(t-\tau)} + \frac{}{1+I}\left\{1-e^{-I_0(1+I)(t-\tau)}\right\} & \tau < t < \tau + T \\ x_4(t) = x_3(\tau+T)e^{-I_0(t-\tau-T)} + 1 - e^{-I_0(t-\tau-T)} & \tau + T < t \end{array}\right\} \quad (24)$$

At points near the cathode, similar waves originate, with smaller amplitudes however. Between A and K there is a point where c is zero and where the relative concentration of X consequently does not change.

For the anode a similar set of equations results. In the same way a diphasic wave is found, with reversed phases, while the amplitudes are appreciably smaller than at the cathode.

2. Constant current of infinitely long duration, which causes no excitation

If through AK is sent a constant current of infinitely long duration, which does not excite, at first we have

$$\frac{dx_1(t)}{dt} = -I_0 x_1(t) + I_0(1+I) \qquad o < t < \tau \tag{25}$$

the solution of which is

$$x_1(t) = 1 + I(1-e^{-I_0 t}) \tag{26}$$

But afterwards

$$\frac{dx_2(t)}{dt} = -I_0(1+I)x_2(t) + I_0(1+I) \qquad \tau < t \tag{27}$$

the solution of which is

$$\begin{aligned} x_2(t) &= x_1(\tau)e^{-I_0(1+I)(t-\tau)} + 1 - e^{-I_0(1+I)(t-\tau)} \\ &= 1 + I(1-e^{-I_0 t})e^{-I_0(1+I)(t-\tau)} \end{aligned} \tag{28}$$

After $x_1(t)$ has risen from unity to $x_1(\tau)$, $x_2(t)$ decreases exponentially to unity again (Fig. 7), which is shown most clearly if we put $x(t) - 1 = A(t)$.

Whence it follows that

$$A_2(t) = A_1(\tau)e^{-I_0(1+I)(t-\tau)} \tag{29}$$

At some distance from the cathode the same thing happens, with smaller amplitude however. At and near the anode a similar thing occurs. Here $x_1(t)$ at first decreases, afterwards increases again.

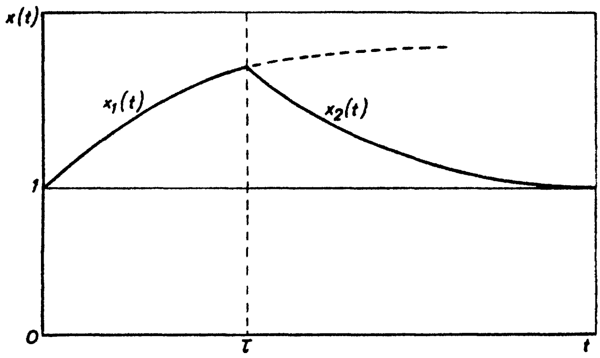


FIG. 7 – Course of the Rel. Conc. of X at the cathode with a constant current of infinite duration ($\tau_2 = 0$).

If we wait long enough, the relative concentration of the matter X will revert to unity along the whole length of the nerve: the nerve has accommodated or adapted itself. This does not mean however, that the former condition has returned everywhere. Although the relative concentration has become unity everywhere, at the cathode accelerated metabolism of the matter X obtains. At the anode metabolism is being retarded. At the cathode

$$\frac{dx(t)}{dt} = - I_0(1+I)x(t) + I_0(1+I) \quad \text{continuously} \tag{30}$$

with

$$x(t) = 1.$$

At the anode

$$\frac{dx(t)}{dt} = -\frac{I_0}{1+I'}x(t) + \frac{I_0}{1+I'} \tag{31}$$

similarly with

$$x(t) = 1.$$

The fact that everywhere $x(t) = 1$ or $\xi(t) = \xi_0$, means that phenomena of Physiological Electrotonus are absent.

3. Rectangular current-pulse, eliciting excitation. "Make excitation".

From the above it now follows that the critical positive amplitude A, which has to be reached for excitation, in any case first obtains at the cathode and that during the first phase in which

$$\frac{dx(t)}{dt} = -I_0x(t) + I_0(1+I) \qquad o < t < T \tag{32}$$

The solution of this equation is

$$x(t) = 1 + I(1-e^{-I_0t}) \tag{33}$$

For excitation

$$1 + I(1-e^{-I_0T}) = 1 + A \quad \text{is consequently required}$$

or

$$I(1-e^{-I_0T}) = A \tag{34}$$

This formula denotes the relation between the current-strength and the so-called utilization-time T.

In case the equation (32) should hold for $o < T < \infty$, there would still be a finite current-strength for $T = \infty$.

Let this be in "biological measure" R_0, the theoretical Rheobase, then

$$R_0 = A \tag{35}$$

and we may write

$$\frac{I}{R_0} = \frac{1}{1-e^{-I_0T}} \tag{36}$$

This formula determines the time-intensity diagram or strength-

duration curve (Fig. 8). It is identical with HILL's and corresponds in many cases remarkably well with the experiments.

HILL's time-constant k is here nothing else but $\frac{1}{I_0}$. Since k is, for the sciatic nerve of the frog, of the order 0.4, it follows that $I_0 = 2.5$

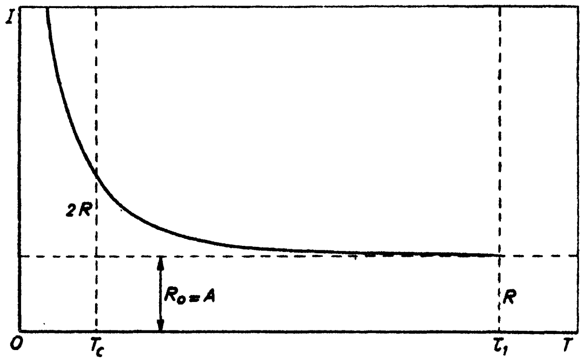


FIG. 8 – Theoretical strength-duration curve for constant-current pulses (threshold-values). T, utilization-time; t_1, H.Z.N.; T, chronaxie; I, intensity and R, rheobase, both in "biological measure"; A, critical amplitude.

(time expressed in σ). The validity of formula (24) is determined by τ. In the case $T > \tau$, dissimilation will decrease the Relative Concentration again for $t > \tau$. So τ is the H.N.Z. and the measured Rheobase R is deduced from

$$R(1 - e^{-I_0\tau}) = A = R_0 \tag{37}$$

or

$$R = \frac{A}{1 - e^{-I_0\tau}}$$

and

$$\frac{R}{R_0} = \frac{1}{1 - e^{-I_0\tau}} > 1 \tag{38}$$

Now for the sciatic of the frog τ is of the order $3\,\sigma$.
For $I_0 = 2.5$ and $\tau = 3$, $e^{-I_0\tau} = e^{-7.5}$ becomes negligible, so that practically $R = R_0$.

For the Chronaxie T_c (with $I = 2R$), introduced by LAPICQUE, the conception of which has proved so useful, we find

$$\frac{2R}{R} = \frac{1}{1-e^{-I_0 T_c}}$$

whence

$$1 - e^{-I_0 T_c} = \tfrac{1}{2} \text{ and } T_c = \frac{lg2}{I_0} \tag{39}$$

For a very short utilization-time T we may substitute $I_0 T$ for $1-e^{-I_0 T}$. From (34) it follows that

$$IT = \frac{A}{I_0} \tag{40}$$

and

$$Q_0 = iT = \frac{A}{cI_0} \tag{41}$$

where Q_0 is the charge which is sent through the nerve during the current-pulse.

The quantity of electricity which has to be sent through the nerve during a utilization-time as long as possible, however, is equal to

$$R\tau = \frac{A\tau}{1-e^{-I_0\tau}}$$

As $e^{-I_0\tau}$ may be neglected, this amount becomes

$$Q_T = \frac{R\tau}{c} = \frac{A\tau}{c} \tag{42}$$

4. Influence of various factors on the magnitudes introduced

In connection with what has been stated on the dependence of the different magnitudes on different parameters, I note that: The resting-values I_0 and L_0, the relaxation-times τ_1 and τ_2, the reserves ϱ_0 which are thought to be constant, and ipso facto the resting-value of X ξ_0, and the critical amplitude A, are all of them determined by the preparation of the experiment. Among the parameters which figure here are, for instance, temperature, percentage of water, preparative treatment with ($K^{\cdot}$) or ($Ca^{\cdot\cdot}$), etc. Examining what sort of

influence these parameters have on the different magnitudes we can presume that

1⁰ Rise of temperature will increase both I_0 and L_0 and possibly decrease τ_1 and τ_2.

2⁰ Desiccation will decrease both I_0 and L_0.

3⁰ Provided it is true that it is (K˙) and (Ca˙˙) ions which help to assimilate and dissimilate acetylcholine, a preparation with Ca will increase I_0 and decrease the resting-concentration ξ_0 and consequently enhance the critical amplitude A. As a matter of fact, the excitability declines by excess of (Ca˙˙), whereas excess of (K˙) in accordance with the preceding would have the reverse result.

From the above it follows, that each preparation has its own magnitudes I_0, L_0, τ_1, τ_2 and A, dependent on the above-mentioned parameters. Since I_0 and A change in the same sense, the quotient $\frac{A}{I_0}$ will within certain limits be probably more or less constant.

This means that for very short current-pulses $iT = \frac{A}{cI_0}$ may be constant for a number of preparations.

It follows further that the product of Chronaxie and Rheobase $RT_c = \frac{A}{I_0} lg 2$, is also constant, a result which in many cases will be found correct, although by no means always, of course.

5. Condenser discharge

If a condenser of the capacity $\boldsymbol{C}$ is charged to a tension $\boldsymbol{E}$ and afterwards discharged via a resistance $\boldsymbol{R}$, the current-strength at the the time t is

$$i = \frac{\boldsymbol{E}}{\boldsymbol{R}} e^{-\frac{t}{\boldsymbol{RC}}} \tag{43}$$

Let $a = \frac{1}{\boldsymbol{RC}}$, in which $\frac{1}{a}$ is the time-constant of the condenser-discharge. It follows that

$$ci = \frac{c\boldsymbol{E}}{\boldsymbol{R}} e^{-at} = Ie^{-at} \tag{44}$$

The equation of metabolism for the cathode consequently becomes

$$\frac{dx_1(t)}{dt} = -I_0 x_1(t) + I_0(1 + Ie^{-at}) \qquad o < t < \tau \tag{45}$$

and its solution is

$$x_1(t) = 1 + \frac{I.I_0}{I_0 - a} \left\{ e^{-at} - e^{-I_0 t} \right\} \qquad o < t < \tau \tag{46}$$

For $t > \tau$, the equation holds

$$\frac{dx_2(t)}{dt} = -I_0 \left\{ 1 + Ie^{-a(t-\tau)} \right\} x_2(t) + I_0(1 + Ie^{-at}) \tag{47}$$

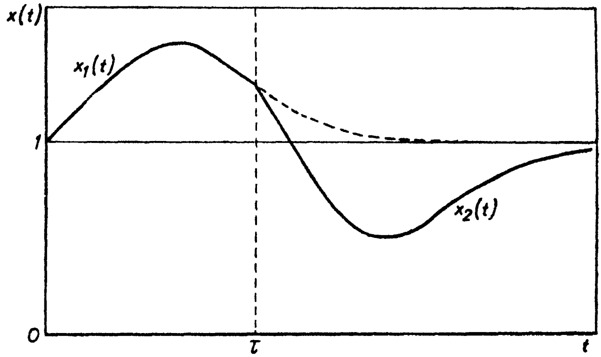


FIG. 9 – Course of the Rel. Conc. of X at the cathode after a condenser-discharge ($\tau_2 = 0$).

with the solution

$$x_2(t) = e^{-I_0 t - \frac{I_0 I}{a} e^{at} \left(1 - e^{-at} \right)} x_1(\tau) + I_0 \int_\tau^t (1 + Ie^{-au}) e^{I_0 u - \frac{I_0 I}{a} e^{-a(u-\tau)}} du \tag{48}$$

If no excitation results, the course of $x(t)$ is as follows (Fig. 9): The function $x_1(t)$ rises from the rest-value 1 to a maximum. This is reached if $\frac{dx_1(t)}{dt} = o$.

From (46) it follows for the corresponding value of t that

$$t_1 = \frac{1}{I_0 - a} lg \frac{I_0}{a}, \tag{49}$$

at least if $t_1 < \tau$.

Hereafter $x_1(t)$ decreases to $x_1(\tau)$.

Now the further course is determined by $x_2(t)$.

While $x_2(\tau) = x_1(\tau)$, $x_2(t)$ will further decrease to below the original value 1, will reach a minimum and afterwards will rise again to unity. So once more the course is diphasic.

Let

$$t_1 = \frac{1}{I_0^{-a}} lg \frac{I_0}{a} \geqq \tau,$$

then $x_1(t)$ has no maximum during the interval $o \leqq t \leqq \tau$ but rises from 1 to

$$x_1(\tau) = 1 + \frac{I.I_0}{I_0^{-a}} \left\{ e^{-a\tau} - e^{-I_0\tau} \right\} \tag{50}$$

Immediately after, according to the course of $x_2(t)$ a decrease to a minimum < 1 occurs and then a rise to unity.

It is therefore clear that excitation can only occur, if the critical amplitude is reached in the first phase, while for the threshold-value of the condensor-tension, the critical amplitude is just reached if $x_1(t)$ reaches its maximum.

For $t_1 < \tau$, we find from (45)

$$o = - I_0(1 + A) + I_0(1 + Ie^{-at_1})$$

or

$$Ie^{-at_1} = A = R_0 \tag{51}$$

Combining this result with (49), we obtain

$$\frac{I}{R_0} = \left(\frac{I_0}{a}\right)^{\frac{1}{\frac{I_0}{a}-1}} = (I_0RC)^{\frac{1}{I_0RC-1}} \tag{52}$$

Because of $I = \frac{cE}{R}$ and $R_0 = \frac{cE_0}{R}$

in which E_0 is the Rheobasic tension, we may substitute for (52)

$$\frac{E}{E_0} = (I_0RC)^{\frac{1}{I_0RC-1}} \tag{53}$$

This is the formula for the "Volt-Capacity curve" for condenser-excitation (Fig. 10).

Since $I_0 = \frac{1}{k}$, in which k is HILL's time-constant, this is exactly the same formula as was deduced by HILL

$$\frac{E}{E_0} = \left(\frac{RC}{k}\right)^{\frac{1}{\frac{RC}{k}-1}} \tag{54}$$

and which had already earlier been proposed by RUSHTON (1931)

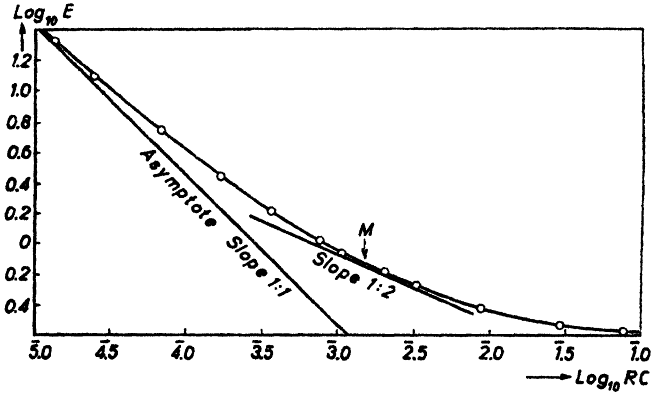


FIG. 10 – Volt-Capacity curve. Frogs nerve at 4° C. From A. V. HILL, *J. Physiol.*, Vol. 83.

and BLAIR (1932) and had been found to be in perfect agreement with experiments by HILL himself (1935, 1936).

The fact that the time intensity curve for direct current stimulation and the volt-capacity curve for condenser-discharges are the same as HILL's for $k = \frac{1}{I_0}$, has as its result that here too

$$\frac{\textit{Chronaxie}}{\textit{RC for } 2 \times \textit{Rheobase}} = \frac{lg\,2}{2} = 0.347 \tag{55}$$

As is well-known, LAPICQUE found experimentally for this quotient the average value 0.37.

It should be noted that from (51) it follows, that the excitation

occurs just at the moment when the tension of the condenser has fallen to the rheobasic tension.

Finally, we have to examine the amount of electricity which is to be sent through the nerve in order to cause excitation, if the condenser discharges in a very short time.

This charge is

$$Q = \int_0^{t_1} \frac{E}{R} e^{-at} dt = \frac{E}{aR}\left(1 - e^{-at_1}\right) \tag{56}$$

From (44) and (51) follows

$$Q = \frac{I}{ca}\left(1 - \frac{A}{I}\right) = \frac{1}{ca} - \frac{A}{ca} \tag{57}$$

We must see what this quantity becomes for $a \to \infty$.

The second term will tend to zero.

In the first term a will also increase if I increases.

Introducing (52)

$$\frac{I}{ca} = \frac{A}{ca}\left(\frac{I_0}{a}\right)^{\frac{1}{\frac{I_0}{a}-1}} = \frac{A}{cI_0}\left(\frac{I_0}{a}\right)^{\frac{\frac{I_0}{a}}{\frac{I_0}{a}-1}} \tag{58}$$

So for $a \to \infty$ the expression (57) tends to

$$Q = \frac{A}{cI_0} \tag{59}$$

This amount is exactly equal to the amount required for very short rectangular current pulses. The constancy of the quantity of electricity at very short utilization-time, independent of the form of the current, is known as the "Constant Quantity Relation" and has been experimentally ascertained by FABER and SWYNGEDAUW (1933), FABRE, QUESNOY, and BERTAUX (1934), SCOTT (1934), BUGNARD and HILL (1935), and ROSENBERG (1935) and forms, as HILL puts it, a crucial test for any excitation-theory.

6. Exponentially rising currents

The phenomena which have always been the most difficult to explain are without doubt the accommodation-phenomena.

Let i be a current-strength which elicits excitation, when supplied as a direct current; as it is, excitation fails to occur, if only the current strength is slowly enough increased towards this strength, viz., is only slowly enough to "creep up".

Du Bois-Reymond has already tried to deduce a law from this phenomenon by assuming that it is not the current itself that irritates but the change of current-strength.

Numerous experiments have proved that this law is incorrect and that another explanation has to be found. Most excitation-theories, however, are deficient in this respect, so that a special cause has to be assumed for the accommodation-phenomena. One theory, viz., Schriever's and Eichler's, tries to deduce accommodation from a certain model, but the model is very artificial and the mathematical treatment difficult and inaccessible. The mathematical theories of Rashevsky, Monnier, and Hill account for it, but, as has been said before, a model-representation is wanting here, which can link up with the physico-chemical occurrence.

In the next pages it will be shown, that the accommodation-phenomena follow automatically from the premised hypothetical equation of metabolism.

The accommodation-phenomena have been experimentally investigated by K. Lucas (1907) *et al.*, who also showed that even a minimal gradient exists below which no excitation is possible, however high the final value of the current-strength may be.

Some investigators (Von Kries, Lucas, Fabre, Blair) used linearly rising currents for the "creeping up", others (Gildemeister, Lapicque, Cardot and Laugier) used exponentially rising currents.

As regards the minimal current gradient, below which no excitation is possible, it has been found first by Lucas.

Fabre called the reverse the so-called "constante linéaire" or C. L. It is the same as Hill's time-constant for the accommodation λ.

Let $\frac{di}{dt}$ be the velocity at which the current-strength rises and i_0 the Rheobase, then the definition will be

$$\text{Minimal current gradient} = \frac{\frac{di}{dt}}{i_0} = \frac{1}{\lambda} \tag{60}$$

Whence it follows that $\frac{di}{dt} = \frac{i_0}{\lambda}$

Because $I = ci$ and $R = ci_0$, we also obtain

$$\frac{dI}{dt} = \frac{R}{\lambda} \tag{61}$$

For exponentially rising currents we may substitute in the equation of metabolism

$$I(t) = I_0 \left\{ 1 + I(1 - e^{-\frac{t}{a}}) \right\} \tag{62}$$

in which a is the time-constant of this exponentially rising current. In the first phase $o < t < \tau$, the equation of metabolism becomes

$$\frac{dx_1(t)}{dt} = - I_0 x_1(t) + I_0 \left\{ 1 + I(1 - e^{-\frac{t}{a}} \right\} \tag{63}$$

In the second phase, the accommodation-phase, obtains

$$\frac{dx_2(t)}{dt} = - I_0 \left\{ 1 + I(1 - e^{-\frac{t-\tau}{a}}) \right\} x_2(t) + I_0 \left\{ 1 + I(1 - e^{-\frac{t}{a}}) \right\} \tag{64}$$

The solutions of these equations are not simple functions. After integration and some arrangements, we find

$$x_1(t) = 1 + I - \frac{I.I_0}{I_0 - \frac{1}{a}} e^{-\frac{t}{a}} + I.I_0 \left(\frac{1}{I_0 - \frac{1}{a}} - \frac{1}{I_0} \right) e^{-I_0 t} \qquad o < t < \tau \tag{65}$$

Then

$$e^{I_0 \left\{ (1+I)t + Ia e^{-\frac{t-\tau}{a}} \right\}} x_2(t) = x_2(\tau) +$$

$$+ \int_\tau^t I_0 \left\{ 1 + I(1 - e^{-\frac{u}{a}}) \right\} e^{I_0 \left\{ (1+I)u + Ia e^{-\frac{u-\tau}{a}} \right\}} du \qquad t > \tau \tag{66}$$

For $t = \tau$ we get $x_2(\tau) = x_1(\tau)$

Introducing $x_2(\tau)$ in (66), we find

$$x_2(t) = e^{-I_0\left\{(1+I)t + Iae^{-\frac{t-\tau}{a}}\right\}}\left\{1 + I - \frac{I_0 I}{I_0 - \frac{1}{a}}e^{-\frac{\tau}{a}} + I_0 I\left(\frac{1}{I_0 - \frac{1}{a}} - \frac{1}{I_0}\right)e^{-I_0\tau}\right\} +$$

$$+ e^{-I_0\left\{(1+I)t + Iae^{-\frac{t-\tau}{a}}\right\}}\int_\tau^t I_0\left\{1 + I(1 - e^{-\frac{u}{a}})\right\}e^{-I_0\left\{(1+I)u + Iae^{-\frac{u-\tau}{a}}\right\}}du \qquad t > \tau \qquad (67)$$

If no excitation occurs, the course of $x(t)$ will be as follows: For $o < t < \tau$, $x_1(t)$ is a monotonically increasing function from 1 to

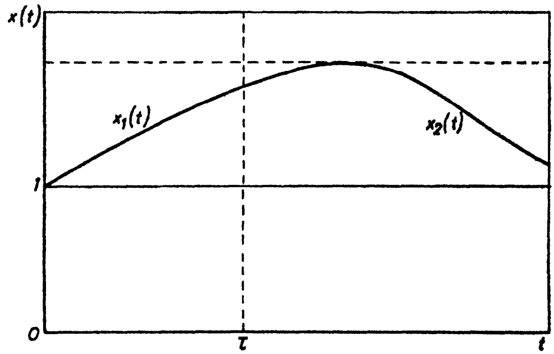


FIG. 11 – Course of the Rel. Conc. of X at the cathode with exponentially increasing currents ($\tau_2 = 0$).

$x_1(\tau)$. Hereafter $x_2(t)$ will at first increase from $x_2(\tau) = x_1(\tau)$, in order to decrease monotonically again to unity, after having reached a maximum (Fig. 11).

It may be possible, that for certain values a and I, the critical amplitude is reached in the first phase. If this does not happen however, excitation may occur all the same at a time $t_1 > \tau$, because $x_2(t)$ is in the beginning still increasing.

The threshold-value of I is then obtained from the condition that the critical amplitude is reached just at the moment when $x_2(t)$ reaches its maximum.

It is clear without comment, that when a increases, I must also be larger, while t_1 too will increase.

I now propose to prove that:

1⁰. *For increasing a, t_1 has a limit.* This has been experimentally ascertained by LAPICQUE (1926), also by GILDEMEISTER (1904, 1913). From HILL's theory it does not necessarily follow, but HILL is able to demonstrate that t_1 is practically always less than four times the H.N.Z.

2⁰. *For increasing a, $\frac{I}{a}$ has a limit.* This means that there is in fact a minimal gradient, below which no excitation can occur, however large I may become.

So I first prove the existence of $\lim\limits_{a \to \infty} t_1(a)$.

Demonstration. For the general equation of metabolism in the second phase

$$\frac{dx_2(t)}{dt} = -I(t-\tau)x_2(t) + I(t),$$

we may write

$$\frac{dx_2(t)}{dt} = -\left\{ I(t) - \tau I'(t-\theta\tau) \right\} x_2(t) + I(t) \qquad o < \theta < 1 \tag{68}$$

This function reaches its maximum when $\frac{dx_2(t)}{dt} = o$ and the maximum is then exactly $1 + A$, so

$$\left\{ I(t_1) - \tau I'(t_1 - \theta\tau) \right\} (1 + A) = I(t_1) \tag{69}$$

From

$$I(t) = I_0 \left\{ 1 + I(1 - e^{-\frac{t}{a}}) \right\}$$

it follows that

$$I'(t) = \frac{I_0 I e^{-\frac{t}{a}}}{a} \tag{70}$$

Whence

$$\left\{ 1 + I(1 - e^{-\frac{t_1}{a}}) - \frac{\tau I}{a} e^{-\frac{t_1 - \theta\tau}{a}} \right\} (1 + A) = 1 + I(1 - e^{-\frac{t_1}{a}}) \tag{71}$$

So we obtain

$$I = \frac{A}{(1+A)\frac{\tau}{a}e^{-\frac{t_1-\theta\tau}{a}} - A(1-e^{-\frac{t_1}{a}})} \tag{72}$$

Now all magnitudes in (72) are positive. Hence

$$\frac{(1+A)\tau e^{-\frac{t_1-\theta\tau}{a}}}{a} > A(1-e^{-\frac{t_1}{a}}) \tag{73}$$

or

$$\left\{ A + \frac{(1+A)\tau}{a} e^{\frac{\theta\tau}{a}} \right\} e^{-\frac{t_1}{a}} > A \tag{74}$$

Because $e^{-\frac{t_1}{a}} < 1$ we have

$$A + \frac{(1+A)\tau}{a} e^{\frac{\theta\tau}{a}} > \left\{ A + \frac{(1+A)\tau}{a} e^{\frac{\theta\tau}{a}} \right\} e^{\frac{t_1}{a}} > A \tag{75}$$

For $a \to \infty$ the left term tends to A, so that the middle term too must tend to A. Since the expression between the brackets tends to A as well, $e^{-\frac{t_1}{a}}$ must tend to 1, in other words

$$\lim_{a\to\infty} \frac{t_1}{a} = o \tag{76}$$

From (75) it follows that

$$e^{-\frac{t_1}{a}} > \frac{1}{1 + \frac{(1+A)\tau}{Aa} e^{-\frac{\theta\tau}{a}}} \tag{77}$$

Hence

$$t_1 < a\, lg \left\{ 1 + \frac{(1+A)\tau}{Aa} e^{\frac{\theta\tau}{a}} \right\} < lg \left\{ 1 + \frac{(1+A)\tau}{Aa} e^{\frac{\tau}{a}} \right\}^a <$$

$$< lg \left\{ 1 + \frac{(1+A)\tau}{Aa} e^{\frac{\tau}{a_1}} \right\}^a \text{ if } a_1 < a \tag{78}$$

We have, however,

$$\lim_{a\to\infty} \left\{ 1 + \frac{(1+A)\tau}{Aa} e^{\frac{\tau}{a_1}} \right\}^a = e^{\frac{(1+A)\tau}{A} e^{\frac{\tau}{a_1}}} \tag{79}$$

so that

$$t_1 < \frac{(1+A)\tau}{A} e^{\frac{\tau}{a_1}} \tag{80}$$

Since t_1, for increasing a, also acquires an increasing value, it follows that $\lim\limits_{a\to\infty} t_1$ exists $(= t_\infty)$.

The evidence for the existence of $\lim\limits_{a\to\infty} \frac{I}{a}$ can be easily given now.

From (72) it follows that

$$\frac{I}{a} = \frac{A}{(1+A)\tau e^{-\frac{t_1-\theta\tau}{a}} - Aa(1 - e^{-\frac{t_1}{a}})} \tag{81}$$

Because $\lim\limits_{a\to\infty} \frac{t_1}{a} = o$ we obtain

$$c\mu = \lim_{a\to\infty} \frac{I}{a} = \frac{A}{(1+A)\tau - At_\infty} \tag{82}$$

For the minimal current gradient we therefore find

$$\frac{c\mu}{R} = \frac{A}{R\left\{(1+A)\tau - At_\infty\right\}} = \frac{1}{\lambda} \tag{83}$$

Since the Rheobase $R = R_0 = A$, for the usual preparations, it follows that

$$\lambda = (1+A)\tau - At_\infty \tag{84}$$

This result would enable us to calculate A, because λ, τ and t_∞ can all be measured. Experiments now show, however, that the measured magnitudes can never agree with relation (84).

Writing out (84)

$$\lambda = \tau - A(t_\infty - \tau), \tag{85}$$

then from the fact that $t_\infty - \tau > o$, it results immediately that $\lambda < \tau$, while experimentally we always find $\lambda > \tau$.

Since, for instance, τ of the sciatic nerve of the frog is about $3\,\sigma$, we should obtain $\lambda < 3\sigma$.

The solution of this disparity might be expected from the fact that the Physiological Electrotonus is not being reckoned with. It might be much more important than was suspected. It will appear, however, that this too, produces values of $\lambda < \tau$. But after the treatment of the case $\tau_1 < \tau_2$, where a similar thing occurs, the theory will be extended somewhat in Ch. IV, and this quantitative difficulty will disappear.

In formula (84) both λ and t_∞ occur and we wish to express both magnitudes in I_0, A, and τ.

In order to achieve this we must use the involved relation (67). From $x_2(t_\infty) = 1 + A$ and (84) we can eliminate t_∞ and an equation with λ as an unknown originates. The occurrence of non-elementary functions makes it impossible, however, to reach a simple expression.

7. Linearly rising currents

It is clear that the treatment of linearly rising currents offers no more difficulties than that of exponentially rising currents, so that I shall omit these also rather involved calculations.

The fact may be mentioned that for the minimal gradient and for the limit of the utilization-time exactly the same results are obtained as the experiments yield.

8. Break-excitation

We cause a current through AK to creep up to a certain strength, so that no excitation occurs and wait sufficiently long, until the nerve has adapted itself. Then we break the current and if the current-strength is high enough, a reaction will occur which starts from the anode: the anode break-reaction. The explanation of this phenomenon, which together with the cathode make-reaction has found such important applications in neurology (PFLÜGER's laws), provided also difficulties in several excitation-theories. HILL's and RASHEVSKY's theories provide a solution by assuming, that the cutting off of a current is identical with the superposing of a virtual counter-current of the same strength. The break-reaction is thus reduced as it were to a make-reaction, while it is assumed, that the threshold-value at the anode, at least in the absence of Physiological

Electrotonus, has remained constant even after the accommodation; an assumption which is indeed essential for the theories mentioned.

A solution of this type is superfluous for the theory developed here. It follows automatically from the model-representation and the appropriate equation of metabolism.

If the current-strength has remained constant sufficiently long, the concentrations of both types of ions will have decreased appreciably at the anode. It is assumed that in that case approximately

$$I(t) = \frac{I_0}{1+c_3 i} \text{ and } L(t) = \frac{L_0}{1+c_4 i} \tag{86}$$

In the absence of Physiological Electrotonus $c_3 = c_4 = c'$ and we obtain

$$I(t) = \frac{I_0}{1+c'i} = \frac{I_0}{1+I'} \text{ and } L(t) = \frac{L_0}{1+c'i} = \frac{L_0}{1+I'} \tag{87}$$

As soon as the nerve has adapted itself, the concentration of the biogenic substance X has reverted to its original resting-value ξ_0, which, by the way, applies to all other points of the nerve. Before the withdrawal of the current the equation of metabolism is therefore

$$\frac{dx(t)}{dt} = -\frac{I_0}{1+I'}\, x(t) + \frac{I_0}{1+I'} \text{ with } x(o) = x(t) = 1 \tag{88}$$

When the current is cut off, the ion-concentrations return to their original values, while through the relaxation-times the assimilation of X is the first to be quickened, for $\tau_2 = o$ instantaneously, and the change in the dissimilation begins only after a time τ_1.

After the current has been cut off, changes in the concentrations of X therefore occur which are determined by the equations

$$\frac{dx_1(t)}{dt} = -\frac{I_0}{1+I'}\, x_1(t) + I_0 \qquad o < t < \tau \tag{89}$$

and

$$\frac{dx_2(t)}{dt} = -I_0 x_2(t) + I_0 \qquad t < \tau \text{ respectively.} \tag{90}$$

The result is that in the first phase $o < t < \tau$, the Relative Concen-

tration of X will rise from unity to $x_1(\tau)$, in order to decrease exponentially in the second phase $t > \tau$.

So the excitation will have to occur during the first phase.

The solution of the first equation is

$$x_1(t) = 1 + I'(1 - e^{-\frac{I_0 t}{1+I'}}) \tag{91}$$

Excitation occurs if

$$x_1(t) = 1 + A$$

Hence

$$I'(1 - e^{-\frac{I_0 t}{1+I'}}) = A \tag{92}$$

Here too, a theoretical Rheobase R_0 is found, if there is to be no change in the dissimilation.

For $t \to \infty$, just as with make-excitation, it is

$$R_0 = A \tag{93}$$

The real Rheobase R′ however, is to be found from the equation

$$R'(1 - e^{-\frac{I_0 \tau}{1+R'}}) = A \tag{94}$$

Now it is questionable if, just as with make-excitation, $e^{-\frac{I_0 \tau}{1+R'}}$ is negligible and it is very well possible that $R' \gg R_0$.

Although the time t has a somewhat different significance than in the formulae for make-excitation—it is the time which elapses between the breaking of the current and the moment of excitation — we can plot a kind of strength-duration-curve:

$$\frac{I'}{R_0} = \frac{1}{1 - e^{-\frac{I_0 t}{1+I'}}} \tag{95}$$

or

$$\frac{R'}{I'} = \frac{1 - e^{-\frac{I_0 t}{1+R'}}}{1 - e^{-\frac{I_0 t}{1+I'}}} \tag{96}$$

The shape of this curve (Fig. 12) resembles the time-intensity curve for make-excitation, but it has one characteristic divergence.

For $I' \to \infty$, t does not tend to zero, but to a finite value $t_0 = \frac{R'}{I_0}$ It is difficult, however, to examine the strength-duration curve experimentally. The time t submerges in the total latent time viz., the time between the break and the occurrence of the muscle-contraction. It seems practically impossible to eliminate the complicating terms in the latent time (propagation-velocity etc.). However, Cluzet (1900), Cardot and Laugier (1912), Laugier (1921), and Solandt (1936) have determined strength-duration curves, but they have quite a different meaning.

By selecting a far-off injured site of the nerve as the cathode, make-excitation is prevented. Now a direct current is made to pass for a given time and the minimum current-strength, which at the break occasions excitation, is measured.

It is clear that this is a totally different problem. What happens at the anode?

The course of the concentration of the matter X is here determined by the following equations, in which it is firstly assumed that $T < \tau$.

$$\left.\begin{aligned} \frac{dx_1(t)}{dt} &= -I_0 x_1(t) + \frac{I_0}{1+I'} && o < t < T \\ \frac{dx_2(t)}{dt} &= -I_0 x_2(t) + I_0 && T < t < \tau \\ \frac{dx_3(t)}{dt} &= -\frac{I_0}{1+I'} x_3(t) + I_0 && \tau < t < \tau + T \\ \frac{dx_4(t)}{dt} &= -I_0 x_4(t) + I_0 && \tau + T < t \end{aligned}\right\} \quad (97)$$

with the solutions

$$x_1(t) = \frac{1 + I' e^{-I_0 t}}{1 + I'} \qquad o < t < T \qquad (98)$$

$$x_2(t) = e^{-I_0(t-T)} x_1(T) + 1 - e^{-I_0(t-T)} \qquad T < t < \tau \qquad (99)$$

$$x_3(t) = e^{-\frac{I_0}{1+I'}(t-\tau)} x_2(\tau) + (1 + I') \left\{ 1 - e^{-\frac{I_0}{1+I'}(t-\tau)} \right\} \qquad \tau < t < \tau + T \qquad (100)$$

$$x_4(t) = e^{-I_0(t-\tau-T)} x_3(\tau + T) + 1 - e^{-I_0(t-\tau-T)} \qquad \tau + T < t \qquad (101)$$

This shows that $x(t)$ at first drops from 1 to $x_1(T)$, then increases exponentially as far as $t = \tau$, afterwards quickly rises above the normal value 1 until $t = \tau + T$, in order to decrease again exponentially to unity.

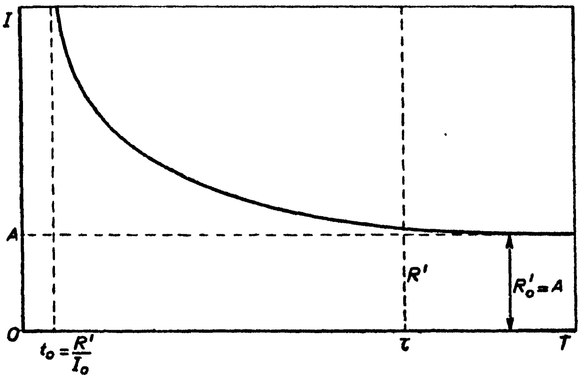


FIG. 12 – Theoretical strength-duration curve for Break-excitation.

Therefore excitation must occur in the third part and for the threshold-value just at the time $\tau + T$.
Hence

$$(1 + I')\left\{1 - e^{-\frac{I_0\tau}{1+I'}}\right\} + e^{-\frac{I_0\tau}{1+I'}} x_2(\tau) = 1 + A$$

Inserting $x_2(\tau)$, we obtain

$$I'(1 - e^{-\frac{I_0\tau}{1+I'}}) - \frac{I'}{1+I'} e^{-I_0(\tau + \frac{T}{1+I'})} (e^{I_0T} - 1) = A \qquad (102)$$

This complicated formula now yields the strength-duration curve for the experiments mentioned. If I is very large and so T small, considering also the smallness of $e^{-I_0\tau}$ for the usual preparations, the formula simplifies to

$$I'\left(1 - e^{-\frac{I_0T}{1+I'}}\right) = A \qquad (103)$$

This is the same formula as (92).

So here too, I' large, requires a finite time T_0 with $T_0 = \frac{R'}{I_0}$.

At the present moment I do not know if this has indeed been discovered. It is certain however, that the formula derived by HILL, in which such a finite time does not exist, does not agree with CARDOT's and LAUGIER's experiments (1912) for very short times. Moreover T_0 may be very small. For $T > \tau$ the equations turn out somewhat differently.

$$\left.\begin{aligned}
\frac{dx_1(t)}{dt} &= -I_0 x_1(t) + \frac{I_0}{1+I'} && o < t < \tau \\
\frac{dx_2(t)}{dt} &= -\frac{I_0}{1+I'}\,x_2(t) + \frac{I_0}{1+I'} && \tau < t < T \\
\frac{dx_3(t)}{dt} &= -\frac{I_0}{1+I'}\,x_3(t) + I_0 && T < t < \tau + T \\
\frac{dx_4(t)}{dt} &= -I_0 x_4(t) + I_0 && \tau + T < t
\end{aligned}\right\} \quad (104)$$

Excitation for the threshold-value of I' must occur at the time $t = \tau + T$. The solutions are respectively.

$$x_1(t) = \frac{1 + I' e^{-I_0 t}}{1 + I'} \qquad o < t < \tau \qquad (105)$$

$$x_2(t) = e^{-\frac{I_0}{1+I'}(t-\tau)} x_1(\tau) + 1 - e^{-\frac{I_0}{1+I'}(t-\tau)} \qquad \tau < t < T \qquad (106)$$

$$x_3(t) = e^{-\frac{I_0}{1+I'}(t-T)} x_2(T) + (1 + I')\left\{1 - e^{-\frac{I_0}{1+I'}(t-T)}\right\} \qquad T < t < \tau + T \qquad (107)$$

$$x_4(t) = e^{-I_0(t-\tau-T)} x_3(\tau + T) + 1 - e^{-I_0(t-\tau-T)} \qquad \tau + T < t \qquad (108)$$

After rearrangements we obtain for the strength-duration curve

$$I'\left(1 - e^{-\frac{I_0\tau}{1+I'}}\right) - \frac{I_0\tau}{1+I'}\, e^{-\frac{I_0 T}{1+I'}}\left(1 - e^{-I_0\tau}\right) = A. \qquad (109)$$

Since $e^{-I_0\tau}$ is negligible for the usual preparations we may also write

$$I'\left(1 - e^{-\frac{I_0\tau}{1+I'}}\right) - \frac{I'}{1+I'}\, e^{-\frac{I_0 T}{1+I'}} = A \qquad (110)$$

For $T \to \infty$ the Rheobase for break-excitation is obtained from

$$R'\left(1 - e^{-\frac{I_0\tau}{1+R'}}\right) = A = R \qquad (111)$$

Therefore, in general $R' > R$.

Finally, a new result proceeds from the theoretical explanation of the break-excitation. The fact, that the Relative Concentration of X at the anode, after the current has been cut off, rises above the resting-value, is described by the equation then holding (89)

$$\frac{dx_1(t)}{dt} = -\frac{I_0}{1+I'}x_1(t) + I_0 \qquad . \qquad 0 < t < \tau$$

The critical amplitude A must be reached not later than for $t = \tau$. If there is one $I_1 = c'i$ at which this happens, there will also be break-excitation for i greater, the excitation having occurred earlier. We can now imagine, that even for $I' = \infty$ the critical amplitude A is reached for $t \leqq \tau$.

For $I_1 = \infty$ the equation (89) becomes

$$\frac{dx_1(t)}{dt} = I_0 \qquad x_1(t) = 1 + I_0 t \qquad 0 < t < \tau \qquad (112)$$

The maximum amplitude, which is reached after $t = \tau$, is therefore $I_0\tau$. So if $A > I_0\tau$, there is certainly no break-excitation. Since A, I_0, and τ are magnitudes which depend on several circumstances like environment, preparation, temperature, and humidity, it may be imagined that such a condition can exist. In the cases when break-excitation occurs experimentally, we find that $A > I_0\tau$.

9. Gap in a constant current

If a constant current is interrupted after the nerve has adapted itself, excitation may occur at break at the anode and at make at the cathode. The first case has, in fact, been treated in section (8).

For excitation occurring at the cathode the following equations hold good:

Before break

$$\frac{dx_0(t)}{dt} = -I_0(1 + I)x_0(t) + I_0(1 + I) \qquad x_0(t) = 1 \qquad (113)$$

During break

$$\left.\begin{array}{ll}\dfrac{dx_1(t)}{dt} = -I_0(1+I)\,x_1(t) + I_0 & o < t < T \\ \text{Hereafter} & \\ \dfrac{dx_2(t)}{dt} = -I_0(1+I)x_2(t) + I_0(1+I) & T < t < \tau \\ \dfrac{dx_3(t)}{dt} = -I_0x_3(t) + I_0(1+I) & \tau < t < \tau + T \\ \dfrac{dx_4(t)}{dt} = -I_0(1+I)x_4(t) + I_0(1+I) & \tau < T < t.\end{array}\right\} \quad (114)$$

Consequently the concentration of X will decline during break, then rise exponentially until $t = \tau$, subsequently increase until $t = \tau + T$ in order to decrease again exponentially to ξ_0 (Fig. 13).

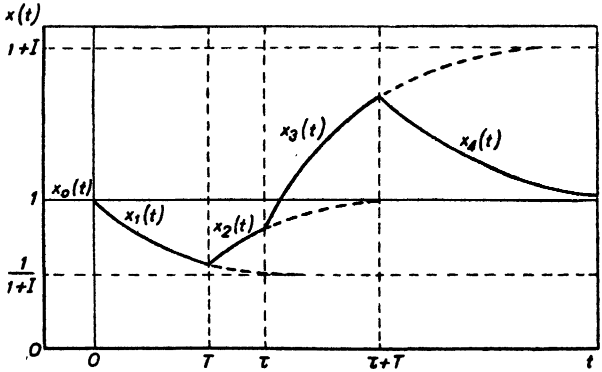


FIG. 13 – Course of the Rel. Conc. of X at the cathode during and after interrupting a constant current. T, time of the gap. ($\tau_2 = 0$).

Excitation for the threshold-value will therefore occur at the time $t = \tau + T$.

The solutions of the equations (114) are as follows:

$$x_1(t) = \frac{1 + Ie^{-I_0(1+I)t}}{1+I} \qquad o < t < T \qquad (115)$$

$$x_2(t) = e^{-I_0(1+I)(t-T)}\,x_1(T) + 1 - e^{-I_0(1+I)(t-T)} \qquad T < t < \tau \qquad (116)$$

$$x_3(t) = e^{-I_0(t-\tau)} x_2(\tau) + (1 + I) \{1 - e^{-I_0(t-\tau)}\} \qquad \tau < t < \tau + T \tag{117}$$

$$x_4(t) = e^{-I_0(1+I)(t-\tau-T)} x_3(\tau + T) + 1 - e^{-I_0(1+I)(t-\tau-T)} \qquad \tau + T < t. \tag{118}$$

The threshold-value of I is obtained from $x_0(\tau + T) = 1 + A$. So

$$I - (1 + I)e^{-I_0T} + e^{-I_0T} x_2(\tau) = A. \tag{119}$$

Introducing $x_2(\tau)$, we find

$$I(1 - e^{-I_0T}) + \frac{I}{1 + I} e^{-I_0\{(1+I)\tau+T\}} \{- 1 + e^{I_0(1+I)T}\} = A. \tag{120}$$

Now the second term is practically negligible for T small and we obtain

$$I\ (1 - e^{-I_0T}) = A = R.$$

So

$$\frac{I}{R} = \frac{1}{1 - e^{-I_0T}}. \tag{121}$$

This is the equation for the strength-duration curve, which is the same as for the ordinary make-excitation and the same as the approximate equation derived by HILL. It only obtains for T small. For $T > \tau$, the equations become

$$\left.\begin{aligned} \frac{dx_1(t)}{dt} &= - I_0(1 + I)x_1(t) + I_0 && o < t < \tau \\ \frac{dx_2(t)}{dt} &= - I_0x_2(t) + I_0 && \tau < t < T \\ \frac{dx_3(t)}{dt} &= - I_0x_3(t) + I_0(1 + I) && T < t < \tau + T \\ \frac{dx_4(t)}{dt} &= - I_0(1 + I)x_4(t) + I_0(1 + I) && \tau + T < t \end{aligned}\right\} \tag{122}$$

with the solutions

$$x_1(t) = \frac{1 + Ie^{-I_0(1+I)t}}{1 + I} \tag{123}$$

$$x_2(t) = e^{-I_0(t-\tau)} x_1(\tau) + 1 - e^{-I_0(t-\tau)} \tag{124}$$

$$x_3(t) = e^{-I_0(t-T)} x_2(T) + (1 + I) \left\{ 1 - e^{-I_0(t-T)} \right\} \tag{125}$$

$$x_4(t) = e^{-I_0(1+I)(t-\tau-T)} x_3(\tau + T) + 1 - e^{-I_0(1+I)(t-\tau-T)}. \tag{126}$$

Since excitation occurs when $x_3(t+T) = 1+A$, we now find for the strength-duration curve

$$I(1 - e^{-I_0\tau}) - \frac{I}{1 + I} e^{-I_0 T} \left\{ 1 - e^{-I_0(1+I_0)\tau} \right\} = A. \tag{127}$$

Since $e^{-I_0\tau}$ and $e^{-I_0(1+I)\tau}$ are negligible, this equation can be reduced to

$$I - \frac{1}{1 + I} e^{-I_0 T} = A. \tag{128}$$

For the Rheobase we find, for $T = \infty$, just as with ordinary make-excitation

$$R = A = R_0.$$

The difference is, that with make-excitation for constant-current pulses, the Rheobase excites after the H.N.Z., while here the Rheobase excites for $T \to \infty$.

10. Alternating current

The treatment of the alternating current excitation cannot but lead to very intricate functions. Examining, for instance, what happens at the cathode, if the current during the first half-period flows from A to K.

The equation for the changes of the concentration of X is

$$\frac{dx(t)}{dt} = - I(t - \tau)x(t) + I(t)$$

How does the last term change? At first

$$I(t) = I_0 \left\{ 1 + I \sin \frac{2\pi(t + \varphi)}{T} \right\}. \tag{129}$$

When $t + \varphi = \frac{T}{2}$ the current reverses. Then follows during half a period

$$I(t) = \frac{I_0}{1 + I \sin \frac{2\pi t}{T}}. \tag{130}$$

Subsequently, during a new half-period

$$I(t) = I_0(1 + I \sin \frac{2\pi t}{T}) \qquad \text{etc.}$$

The coefficient of $x(t)$, $I(t-\tau)$, however at first remains I_0, viz., for $o < t < \tau$. Afterwards the same asymmetrical changes occur as was the case with the last term.

In the meantime $x(t)$ changes repeatedly. What happens depends almost entirely on the relation of τ to T.

Let $T \ll \tau$.

If during the first partial half-period the critical amplitude A is not reached (in that case there is no initial contraction), the final value of $x(t)$ is larger than 1.

After this the current inverts and during the next half-period $x(t)$ will decrease again, not to the original value however, but perhaps to one greater than, perhaps less than 1. After this the current again reverses and now $x(t)$ will rise again for half a period etc.

At the anode, at the same times, oppositely-directed changes occur. It is clear that it is thus possible that several periods are to elapse, before the critical amplitude is reached. This is exactly what GILDEMEISTER (1930), contrary to classical theories, has discovered for alternating high-frequency currents. A great number of periods must elapse before excitation occurs: the effect of a cathodal half-cycle is not neutralized by the subsequent anode half-wave.

GILDEMEISTER suggested, that a kind of rectification takes place. The phenomenon finds its natural explanation in the equation of metabolism however.

If T is not much smaller than τ, matters will become even more intricate, because in that case τ, as a second phase-difference in the coefficient of $I(t)$, begins to complicate things.

A few predictions can be made, however, without mathematical elaboration. For $T \ll \tau$, I will in general be greater as T grows

smaller. This is a result of the Constant Quantity Relation. If however $T \gg \tau$, the accommodation-period will fairly soon become significant and the effect of the alternating current will in its parts show the same sort of peculiarities as the effect of exponentially rising currents. If T increases, I will increase too.

The optimal frequency N_{opt}, for which I is minimal, will be somewhere near $N = \frac{1}{\tau}$. This too, fits in with the experimental results,

VON KRIES (1884), LULLIES (1929, 1930), ACHELIS (1930), RENQUIST and KOCH (1930), and COPPEE (1934) have obtained values of N_{opt} varying from 50 to over 200.

If $T \ll \tau$, the calculation of the special case when the current starts just at the beginning of a period ($\varphi = o$), produces an important result. From the equation

$$\frac{dx(t)}{dt} = -I_0 x(t) + I_0(1 + I \sin \frac{2\pi t}{T}) \quad o < t < \frac{T}{2} \tag{131}$$

it follows that

$$x(t) = 1 + I_0 I e^{-I_0 t} \int_0^t \sin \frac{2\pi u}{T} e^{I_0 u} du$$

or

$$x(t) = 1 + \frac{I_0 I e^{-I_0 t}}{I_0^2 + (\frac{2\pi}{T})^2} \left\{ \sin \frac{2\pi t}{T} - \frac{2\pi}{I_0 T} \cos \frac{2\pi t}{T} + \frac{2\pi}{I_0 T} \right\}_{o<t<\frac{T}{2}}. \tag{132}$$

This function may have a maximum for $t_1 < \frac{T}{2}$.

For threshold-excitation this ought to be exactly equal to $1 + A$. From (131) it then follows that

$$o = -I_0(1 + A) + I_0 + I_0 I \sin \frac{2\pi t_1}{T}$$

or

$$\sin \frac{2\pi t_1}{T} = \frac{A}{I}. \tag{133}$$

This is only possible if $\frac{A}{I} < 1$, a condition which is certainly satisfied if T is small enough.

Inserting (133) into (132), we obtain

$$\frac{I.I_0^2 e^{-\frac{I_0\tau}{2\pi}\arc\sin\frac{A}{I}}}{I_0^2 + (\frac{2\pi}{T})^2} \left\{ \frac{A}{I} + \frac{2\pi}{I_0 T} \sqrt{1 - \frac{A}{I^2}} + \frac{2\pi}{I_0 T} \right\} = A\,. \qquad (134)$$

If T is very small, it follows that $\frac{A}{I} \sim o$ and $t_1 = \frac{T}{2}$, in other words, exactly half the period is active.

Then (134) is reduced to

$$\frac{IT}{\pi} = \frac{A}{I_0}\,. \qquad (135)$$

Since $\frac{IT}{\pi}$ is precisely the amount of electricity which during half the period flowed through the nerve, evidence is again given that the Constant Quantity Relation has been satisfied. The time-constant k from HILL's theory was $\frac{1}{I_0}$. Because of $A = R$, we may therefore write (135) as follows

$$\frac{I}{R} = \pi nk\,. \qquad (136)$$

This is a very important result, for from HILL's theory it followed that

$$\frac{I}{R} = 2\pi nk\,. \qquad (137)$$

Now KATZ has demonstrated that for frequencies between 5,000 and 10,000 cycles per sec precisely (136) holds good and not the double value predicted by HILL.

Let $T \gg \tau$ and let us consider again the special case when the current starts flowing at the exact moment that a period begins, we firstly obtain

$$\frac{dx_1(t)}{dt} = -\, I_0 x_1(t) + I_0(1 + I\sin\frac{2\pi t}{T})\,. \qquad o < t < \tau \qquad (138)$$

Then obtains

$$\frac{dx_2(t)}{dt} = -\, I_0 \left\{ 1 + I\sin\frac{2\pi(t-\tau)}{T} \right\} x_2(t) + I_0(1 + I\sin\frac{2\pi t}{T})_{\tau<t} \qquad (139)$$

Just as with the exponentially rising and linearly rising currents excitation will appear, for T large enough, in the linearly rising first part of the half-wave. Since threshold-excitation occurs if $x_2(t)$ passes through a maximum, the utilization-time is in general obtained from (139)

$$I_0 \left\{ 1 + I \sin \frac{2\pi (t_1 - \tau)}{T} \right\} (1 + A) = I_0 (1 + I \sin \frac{2\pi t_1}{T}) . \qquad (140)$$

For T large enough, we may simplify (140) to

$$I_0 \left\{ 1 + \frac{2\pi I (t_1 - \tau)}{T} \right\} (1 + A) = I_0 (1 + \frac{2\pi I t_1}{T}) \qquad (141)$$

whence

$$t_1 = \frac{\tau(1 + A)}{A} - \frac{2\pi T}{I} . \qquad (142)$$

For T very large we have, therefore

$$\frac{2\pi T}{I} = \frac{\tau(1 + A)}{A} - t_\infty = \text{constant.}^* \qquad (143)$$

We may put this constant $= \frac{2}{k'R}$

Hence, in connection with $T = \frac{1}{n}$

$$\frac{I}{R} = \frac{\pi k'}{n} \qquad (144)$$

So, for high frequencies, I is proportional to n, for low frequencies inversely proportional.

11. Excitability

The excitability at some point N of a nerve I define as

$$P = \frac{1}{Q}$$

in which Q is the quantity of electricity which, during a current-pulse of very short duration, entering at some far-off periferal point of the nerve and leaving it at N, causes excitation. This definition is therefore intimately connected with the Constant Quantity Relation.

* As t_1 will, just like with exponentially rising currents, tend to a limit t_∞ for very large T.

If the nerve has adapted itself to a certain resting-condition, the Relative Concentation of X will everywhere be 1, and as in (41) for very short current-pulses we have

$$Q_0 = \frac{A}{cI_0} \text{ and } P = \frac{cI_0}{A}. \tag{145}$$

Considering the case when a subliminal current of any type is sent through part of the nerve and superposing at a given moment t_1 a very short test shock, which is just strong enough to excite at N, the current then being cut-off, the following equations obtain:

$$\left.\begin{aligned} \frac{dx_1(t)}{dt} &= - I(t-\tau)x_1(t) + I(t) & o < t < t_1 \\ \frac{dx_2(t)}{dt} &= -I(t-\tau)x_2(t) + I(t) + I_0 I & t_1 < t < t_1 + T \end{aligned}\right\} \tag{146}$$

in which $I = ci$, where i is the intensity of the test-shock and T its duration.

Suppose t_1 is not a moment at which in $n_1(t)$ a discontinuity in the first derivate just occurs, we then obtain

$$e^{\int_{t_1}^{t} I(u-\tau)du} x_2(t) = x_1(t_1) + \int_{t_1}^{t} I(u) e^{\int_{t_1}^{u} I(v-\tau)dv} du + I.I_0 \int_{t_1}^{t} e^{\int_{t_1}^{u} I(v-\tau)dv} du. \tag{147}$$

Excitation occurs for $t = t_1 + \tau$ and in that case $x_2(t_1 + T) = 1 + A$ So

$$e^{-\int_{t_1}^{t_1+T} I(u-\tau)du} \left\{ A_N(t_1) + 1 + \int_{t_1}^{t_1+T} I(u) e^{\int_{t_1}^{u} I(v-c)dv} du + I.I_0 \int_{t_1}^{t_1+T} e^{\int_{t_1}^{u} I(v-\tau)dv} du \right\} = 1 + A. \tag{148}$$

Since $I(u)$ is determined by the conditioning current, $I(u)$ is limited. If T becomes very small

$$e^{-\int_{t_1}^{t_1+T} I(u-\tau)du} \to 1 \quad \text{and} \quad \int_{t_1}^{t_1+T} I(u) e^{\int_{t_1}^{u} I(v-\tau)dv} du \to o.$$

Since T is very small during the test-shock, $I(t-\tau)$ will hardly change and we may therefore put $I(t-\tau) = I(t_1-\tau)$.

In that case however

$$\int_{t_1}^{t_1+T} e^{\int_{t_1}^{u} I(v-\tau)dv} du = \int_{t_1}^{t_1+T} e^{(u-t_1)I(t_1-\tau)} \cdot du = \frac{1-e^{TI(t_1-\tau)}}{I(t_1-\tau)} \sim T. \tag{149}$$

Thus (148) is reduced to

$$I_0 IT = A - A_N(t_1)$$

and for T very small, we obtain

$$IT = \frac{A - A_N(t_1)}{I_0} \text{ or } iT = \frac{A - A_N(t_1)}{cI_0}$$

and in general

$$P(t) = \frac{cI_0}{A - A_N(t_1)}, \tag{150}$$

in other words: the excitability at a point N of a nerve at a certain moment t_1 is inversely proportional to the difference of the critical amplitude and the momentary amplitude of the Relative Concentration of X at the point.

12. The experiments of Erlanger and Blair

From the preceding reflections on excitability proceeds the possibility of examining by means of short test-shocks what sort of changes occur in the concentration of the biogenic excitatory matter X at a certain point, if a current of some type or other passes or has passed through part of the nerve. It has long been known that during and after a subliminal current, certain changes occur at the different points of the nerve.

Keith Lucas used the term "Local Excitatory Disturbance". The conception of "état d'excitation" defined by Monnier has also been generally adopted.

According to the preceding statements, the état d'excitation can be measured by the relative concentration of X. During the resting-state the latter is 1. If it is greater than 1, the excitability has been increased; if it is less than 1, the excitability has been diminished.

Experiments have been made to measure the changes of condition by ERLANGER and BLAIR (1931) (Fig. 14).

After a subliminal direct current has been put in circuit, at different moments a short test-shock is superimposed, the direct current is cut off each time immediately afterwards and the strength of the test-shock, just strong enough to excite, is determined.

ERLANGER's and BLAIR's experiments demonstrate, that the état d'excitation rises exponentially from the resting-value to a certain

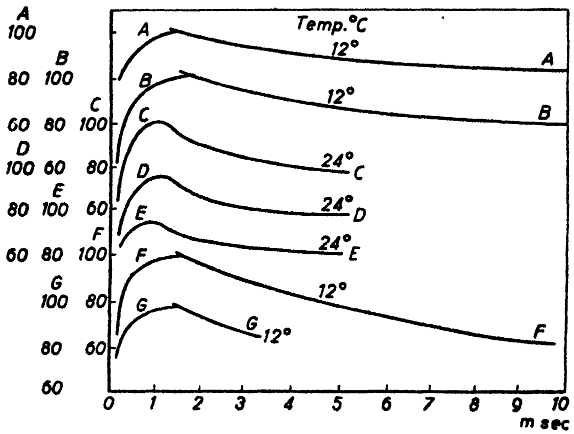


FIG. 14 – Changes of the excitability after the closing of a subliminal direct current of 90% rheobasic strength and at various temperatures. Ordinates: percentages of the maximal excitability. From ERLANGER and GASSER, *Electric signs of nervous activity*, Philadelphia-London 1937.

maximum, which is reached just after the H.N.Z., and then returns gradually to the original resting-value.

Comparing these results with what was derived in Section 2 about the subliminal direct current of infinitely long duration, we obtain the most striking agreement.

For we had obtained for $x(t)$

$$\left.\begin{aligned} x_1(t) &= 1 + I(1 - e^{-I_0 t}) = 1 + ci(1 - e^{-I_0 t}) \qquad & 0 < t < \tau \\ x_2(t) &= 1 + Ie^{-I_0(t-\tau)}(1 - e^{-I_0\tau}) = 1 + cie^{-I_0(t-\tau)}(1 - e^{-I_0\tau}) \qquad & t > \tau \end{aligned}\right\} \quad (151)$$

The gradual decrease of $x(t)$ to the original resting-value of course occurs only in the absence of Physiological Electrotonus.

13. The "état d'excitation" after a short current-pulse

If, through AK a very short current-pulse is sent, the Relative Concentration of X undergoes the following changes, which can be deduced from Section 1. Through the current-pulse, the Relative Concentration suddenly obtains the value $1 + A_0$. Let Q_0 be the charge of the current pulse sent through the nerve, it then follows that $A_0 = cI_0Q_0$.

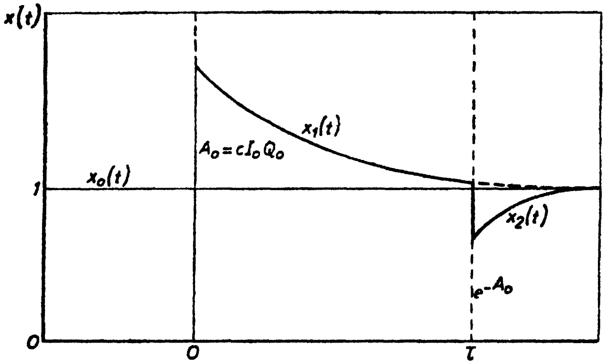


FIG. 15 – Course of the Rel. Conc. of X at the cathode after a constant-current pulse of negligible duration ($\tau_2 = 0$).

Subsequently the Relative Concentration decreases during the H.N.Z. τ as far as $1 + A_0e^{-I_0\tau}$, so practically to 1.

Now a sudden decrease occurs to

$$(1 + A_0e^{-I_0\tau})\, e^{-I_0IT} = (1 + A_0e^{-I_0\tau})\, e^{-cI_0Q_0}$$

so practically to $e^{-cI_0Q_0} = e^{-A_0}$

Finally the Relative Concentration rises again exponentially to 1 (Fig. 15). The excitability enhanced by the current pulse decreases therefore, at first, exponentially. The phenomenon, in which the excitability subsequently temporarily decreases a little, is called "post-cathodal depression" (ERLANGER and BLAIR).

Experiments to measure the decline of excitability after a short

current pulse by means of succesive test-shocks, have been made by RUSHTON and by KATZ.

A few deviations from the theory are found in so far that for $A_0 > \frac{1}{2}A$ the decrease of excitability is not exactly exponential, but at first more gradual.

14. Changes of the Rheobase after accommodation

In the experiments described above, the changes of excitability are measured by very short test-shocks.

Attempts have also been made to determine these changes by

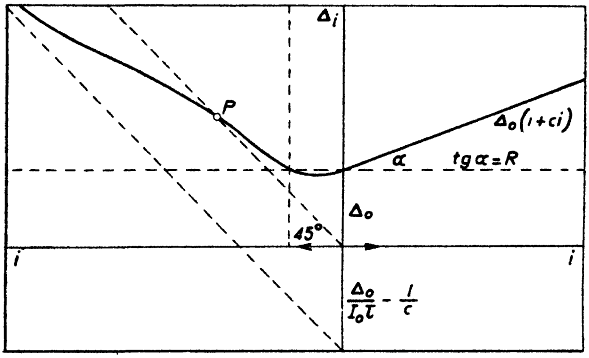


FIG. 16 – First theoretical explanation of CHWEITZER's scheme. Ordinate: threshold-current (test current). – Abscissa: strength of the conditioning current. To the right in the same direction as the test-current, to the left in the opposite direction.

examining how the Rheobase changes if it is superposed on a constant current of the same or opposite direction. The plan was to determine especially the influence of the Physiological Electrotonus (CHWEITZER, Fig. 17). It appears that the Rheobase with currents of the same direction remains—to a certain extent—more or less constant and with stronger currents gradually increases. These findings have led to the assumption that in the absence of Physiological Electrotonus the Rheobase should be constant for adapted nerves, in other words, that the excitability can just as well be measured through test-shocks as through the Rheobase.

HILL's theory for instance starts expressly from this supposition.

When the Rheobase begins to rise at greater current-strengths, he considers this rise as an expression of electronic changes. The latter are not accounted for by his theory.

In the theory expounded here the situation is quite different. We send, if necessary after creeping up, a constant current i through AK and wait sufficiently long until the nerve has accommodated itself. If we now superimpose a current Δ_i in the same direction,

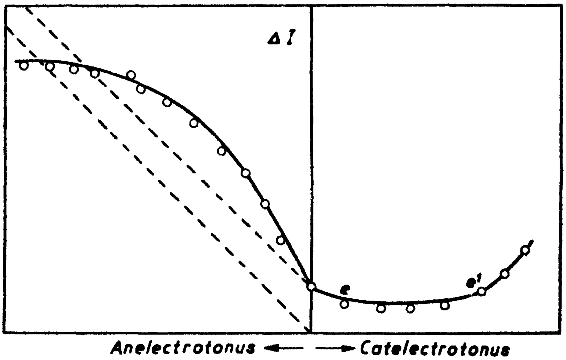


FIG. 17 – CHWEITZER's scheme. Abscissa: Strength of conditioning current. Ordinate: Strength of added threshold current. – The scheme means to demonstrate the electrotonic changes of excitability caused by the conditioning polarising current. From A. CHWEITZER, *Ann. Physiol.*, Vol. 13 (1937).

which is just strong enough to excite, Δ_i will then be the Rheobase after accommodation. Excitation will occur at the cathode.

Before the extra current at the cathode the equation

$$\frac{dx_0(t)}{dt} = - I_0(1 + I)x_0(t) + I_0(1 + I) \qquad (152)$$

held, in which $I = ci$.

As soon as the extra current passes however, we have

$$\frac{dx_1(t)}{dt} = - I_0(1 + I)x_1(t) + I_0(1 + I + R_i) \qquad (153)$$

in which $R_i = c\Delta_i$.

Putting $I_0' = I_0(1 + I)$ we may write

$$\frac{dx_1(t)}{dt} = -I_0'x_1(t) + I_0'\left(1 + \frac{R_i}{1+I}\right). \tag{154}$$

Hence for the new Rheobase (cf. 33)

$$\frac{R_i}{1+I} = \frac{R_0}{1 - e^{-I_0(1+I)\tau}}. \tag{155}$$

This will become practically

$$\frac{R_i}{1+I} = R_0$$

So

$$\Delta_i = (1 + ci)\Delta_0, \tag{156}$$

in which $R_0 = c\Delta_0$ is the ordinary Rheobase in biological measure and Δ_0 the Rheobase in electrical measure.

If the extra current is superposed in the opposite direction, the excitation will occur at the anode.

After accommodation the equation obtains

$$\frac{dx_0(t)}{dt} = -\frac{I_0}{1+I'}x_0(t) + \frac{I_0}{1+I'} \tag{157}$$

As soon as the extra current continues however

$$\frac{dx_1(t)}{dt} = -\frac{I_0}{1+I'}x_1(t) + I_0(1 + R_i - I) \tag{158}$$

in which $I = ci$ and $I' = c'i$.

Let $\frac{I_0}{1+I'} = I_0''$, we then find

$$\frac{dx_1(t)}{dt} = -I_0''x_1(t) + I_0''(1 + I')(1 + R_i - I). \tag{159}$$

For threshold-excitation should have

$$(1 + I')R_i + (1 + I')(1 - I) = \frac{R_0}{1 - e^{-\frac{I_0\tau}{1+I'}}} + 1 \tag{160}$$

or

$$R_i = \frac{R_0}{(1+I')(1-e^{-\frac{I_0\tau}{1+I'}})} + \frac{1-(1+I')(1-I)}{1+I'}$$

or

$$\Delta_i = \frac{\Delta_0}{(1+c'i)(1-e^{-\frac{I_0\tau}{1+c'i}})} + \frac{1-(1+c'i)(1-ci)}{c(1+c'i)}, \qquad (161)$$

equations which cannot, in general, be simplified any more.

For high values of I we obtain

$$\Delta_i = \frac{\Delta_0}{I_0\tau} - \frac{1}{c} + i \qquad (162)$$

Recording the results obtained in a scheme of the type drawn up by CHWEITZER during his investigations into the changes of excitability according to the method elaborated above, we obtain Fig. 16.

From the above it follows that:

Although the excitability of the accommodated nerve, measured by test-shocks, is consequently constant everywhere if electrotonic changes are absent, the Rheobase increases for the cathode as well as for the anode with the "conditioning current" so that it may be said, that strong currents lead to non-excitability in the sense of very high threshold-values.

This phenomenon is known for the cathode as WERIGO's cathodal depression. This cathodal-depression is, of course, a different thing from the previous transient post-cathodal depression, obtained by ERLANGER and BLAIR for subliminal currents.

CHWEITZER's scheme (Fig. 17) only referred to the cases in which Physiological Electrotonus was present. In my opinion the scheme also holds, if electrotonic phenomena are absent. But the agreement with the scheme mostly used in the literature is not perfect. Instead of rising linearly with i in the case of catelectrotonus, Δ_i initially decreases to a flat minimum, the "electrobase", and then rises afterwards.

In Chapter IV, where the equation of metabolism will be generalized, the corrected formula will show that this flat minimum can be predicted by the theory as well, and this will be one of the most important results.

b. The influence of the Physiological Electrotonus

$(c_1 < c_2,\ c_3 < c_4)$

1. The general equation

Taking the defined Physiological Electrotonus into account, we have to start from the general equation

$$\frac{d\xi(t)}{dt} = -I(t-\tau)\xi(t) + L(t)\rho_0. \tag{163}$$

Now, for a current of a given form $i(t)$ at the cathode, the equations

$$\left.\begin{aligned} I(t) &= I_0\left\{1 + c_1 i(t)\right\} \\ \text{and} \quad I(t) &= I_0\left\{1 + c_1 i(t)\right\} \quad \text{held,} \end{aligned}\right\} \tag{164}$$

in which for catelectrotonus, $\frac{c_2}{c_1} > 1$.

For (163) we may substitute

$$\frac{d\xi(t)}{dt} = -I_0\left\{1 + c_1 i(t-\tau)\right\}\xi(t) + L_0\left\{1 + c_2 i(t)\right\}\varrho_0 \tag{165}$$

Because $\frac{\xi_0}{\varrho_0} = \frac{L_0}{I_0}$, we have $L_0\varrho_0 = I_0\xi_0$.

Putting again $x(t) = \frac{\xi(t)}{\xi_0}$, the Relative Concentration of X, we find that (165) becomes

$$\frac{dx(t)}{dt} = -I_0\left\{1 + c_1 i(t-\tau)\right\}x(t) + I_0\left\{1 + c_2 i(t)\right\} \tag{166}$$

For the anode

$$\frac{dx(t)}{dt} = -\frac{I_0}{1 + c_3 i(t-\tau)}\,x(t) + \frac{I_0}{1 + c_4 i(t)} \tag{167}$$

Here, $\frac{c_4}{c_3} > 1$ for anelectrotonus.

With the help of these equations it is, furthermore, possible to examine all cases discussed in which the Electrotonus may play a part.

2. Cases in which the Physiological Electrotonus has no influence

From the equations (166) and (167) it follows directly that the inequality of the constants c_1 and c_2, c_3 and c_4, has no influence, if the phenomena discussed occur within the H.N.Z. τ.

In the first place, the strength-duration curve is retained for constant current pulses

$$I(1 - e^{-I_0T}) = A = R_0$$

in which the theoretical Rheobase R_0 is practically always identical with the measured Rheobase R, so that

$$\frac{I}{R} = \frac{1}{1 - e^{-I_0T}}.$$

Hence, we find in so many cases such a good agreement between theory and experiment.

At the same time it appears, that the Constant Quantity Relation is not influenced by the inequality of the constants c either and that is why the definition of excitability need not be altered either. The condenser-discharges too, work their effects within the H.N.Z. The Volt-Capacity curve

$$\frac{\boldsymbol{E}}{\boldsymbol{E}_0} = (I_0\boldsymbol{RC})^{\frac{1}{I_0\boldsymbol{RC}-1}}$$

remains therefore exactly the same as does the ratio

$$\frac{\text{Chronaxie}}{\boldsymbol{RC} \text{ for twice Rheobase}} = 0.347$$

Finally, what has been said regarding excitation through alternating currents of very high frequency holds good, in other words, the important result $\frac{R}{I} = \pi n k$.

In all other cases the accommodation plays a part and the inequality of the constants asserts itself and electrotonic complications may occur.

3. Subliminal constant current of finite duration

Let the duration of the constant current be $< \tau$, the change of the Relative Concentration of X for $t < \tau$ will then be independent of the inequality of c_1 and c_2. For $t > \tau$ the fall of the Relative Concentration will not be so low, so that the post-cathodal depression diminishes and may possibly disappear. For t sufficiently large the excitability will become normal again. The Relative Concentration tends to 1.

4. Subliminal constant current of infinitely long duration. Pflüger's scheme

With a constant current of infinite duration, the course of the excitability during the time $t \leqq \tau$ remains also equal to a course without Physiological Electrotonus. At the moment $t = \tau$ the excitability is maximal at the cathode. Afterwards it slowly decreases however, and the Relative Concentration of X does not return to the resting-value 1, but to the value

$$x_i = \frac{1 + c_2 i}{1 + c_1 i} > 1$$

Here therefore cathelectrotonus obtains. The excitability has been enhanced.

At the anode changes of the same kind, but of opposite direction occur. The Relative Concentration of X here begins at first to decline until the the moment $t = \tau$, in order to rise gradually to the final value

$$x_i' = \frac{1 + c_3 i}{1 + c_4 i} < 1$$

Here therefore anelectrotonus occurs and the excitability has been diminished.

Now the relations

$$\left.\begin{aligned} I(t) &= I_0(1 + c_1 i) \\ L(t) &= L_0(1 + c_2 i) \end{aligned}\right\} \text{ at the cathode}$$

$$\left.\begin{aligned} I'(t) &= \frac{I_0}{1 + c_3 i} \\ L'(t) &= \frac{L_0}{1 + c_4 i} \end{aligned}\right\} \text{ at the anode}$$

are suppositions which, it is true, meet the needs excellently well, but in any case must be considered approximations. The exact formulae could only be supplied as soon as the structure of nerve should be so well known that the changes of the ion-concentrations by the current along the nerve could be calculated from point to point, interpolarly as well as extrapolarly, as functions of i.

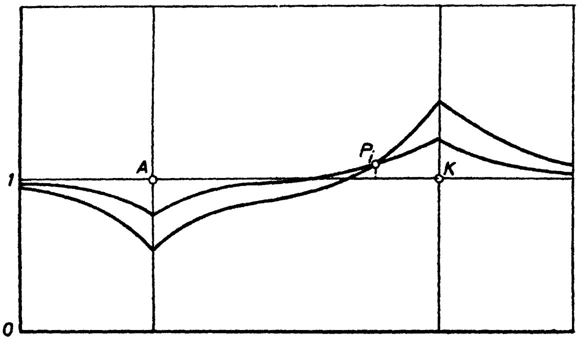


FIG. 18 – Scheme of the possible course of the Rel. Conc. of the various kinds of cations along the nerve by a polarising current through AK, in order to explain the PFLÜGER's scheme.

In this study no attempt has been made to produce a model thereof. On the other hand it may be asserted, that extrapolarly from the cathode x_i will gradually decrease to 1, the further we move from the cathode, while likewise extrapolarly from the anode x_i' will more and more increase to 1. Finally, somewhere between A and K there will be a point P_i, at which the relative concentrations of the two kinds of ions are equal. Here the Relative Concentration of X remains 1.

We may picture this to ourselves almost as in the scheme of Fig. 18.

The correct formulae would then show, that for increasing i the point P_i moves more and more towards K. Apart from the fact that through ignorance of the exact distributive functions of the two kinds of ions the latter cannot be proved. However, the excitability increasing with i at the cathode and the depression at the anode, also increasing with i and the extrapolar decline of both, explain a great deal of PFLÜGER's scheme fairly well.

5. Chweitzer's scheme

The theoretical explanation of CHWEITZER's scheme has been treated, regarding the absence of Physiological Electrotonus, on p. 73. The general treatment will now be as follows: Before the extra current (the Rheobase Δ_i) for the cathode the equation holds:

$$\frac{dx_0(t)}{dt} = - I_0(1 + c_1 i)x_0(t) + I_0(1 + c_2 i) \qquad (168)$$

with the resting-value

$$x_0(\infty) = \frac{1 + c_2 i}{1 + c_1 i}$$

We first put $\frac{c_2}{c_1} < 1 + A$, for should $\frac{c_2}{c_1} \geqq 1 + A$ with increasing i, even after careful creeping up, a state would result in which the resting-value of X would rise above the critical value. In that case a tetanic contraction would be the result.

As soon as the extra-current passes

$$\frac{dx_1(t)}{dt} = - I_0(1 + c_1 i)x_1(t) + I_0(1 + c_2 i + c_2\Delta_i) \qquad (169)$$

with the solution

$$x_1(t) = \frac{1 + c_2 i}{1 + c_1 i} e^{-I_0(1+c_1 i)t} + \frac{1 + c_2 i + c_2\Delta_i}{1 + c_1 i} \left\{ 1 - e^{-I_0(1+c_1 i)t} \right\} \qquad (170)$$

Excitation occurs if $x_1(\tau) = 1 + A$.

So that after rearrangements

$$\frac{1 + c_2 i}{1 + c_1 i} + \frac{c_2\Delta_i}{1 + c_1 i} \left\{ 1 - e^{-I_0(1+c_1 i)\tau} \right\} = 1 + A = 1 + R = 1 + c_2\Delta_0 \qquad (171)$$

Hence

$$\Delta_i = \frac{-(1+c_2 i)+(1+c_1 i)(1+c_2\Delta_0)}{c_2\left\{1-e^{-I_0(1+c_1 i)\tau}\right\}} \tag{172}$$

Since $e^{-I_0(1+c_1 i)\tau} \sim o$, again

$$\Delta_i = \frac{-(1+c_2 i)+(1+c_1 i)(1+c_2\Delta_0)}{c_2} = \Delta_0 + \left(c_1\Delta_0 + \frac{c_1}{c_2} - 1\right)i \tag{173}$$

This goes to show that the superposed Rheobase rises linearly from Δ_0, for from $\frac{c_2}{c_1} < 1 + A = 1 + c_2\Delta_0$ it follows that $c_1\Delta_0 + \frac{c_1}{c_2} - 1 > o$. This again is, in general, not quite in accordance with the experimental results where Δ_i at first decreases to a flat minimum and rises afterwards to ever-increasing values (Fig. 17).

In case of $\frac{c_2}{c_1} > 1 + A$, Δ_i will decrease linearly from Δ_0.

If $$\frac{1+c_2 i}{+\,c_1 i} = 1 + A \quad \text{or} \quad i = \frac{c_2\Delta_0}{c_2-(1+c_2\Delta_0)c_1},$$

the extra current will be zero. At this moment a tetanic contraction will occur.

For the Rheobase opposed to the conditioning current, before the moment the extra current is closed, at the anode obtains:

$$\frac{dx_0(t)}{dt} = -\frac{I_0}{1+c_3 i}\,x_0(t) + \frac{I_0}{1+c_4 i} \tag{174}$$

in which the resting value after accommodation is

$$x_0(\infty) = \frac{1+c_3 i}{1+c_4 i} < 1$$

As soon as the extra current begins to flow we have

$$\frac{dx_1(t)}{dt} = -\frac{I_0}{1+c_3 i}\,x_1(t) + I_0(1+c_2\Delta_i - c_2 i) \tag{175}$$

whence

$$x_1(t) = \frac{1+c_3 i}{1+c_4 i}\,e^{-\frac{I_0 t}{1+c_3 i}} + (1+c_3 i)(1+c_2\Delta_i - c_2 i)\left(1-e^{-\frac{I_0 t}{1+c_3 i}}\right) \tag{176}$$

For $t = \tau$, we have $x_1(\tau) = 1 + A$, so

$$\frac{1 + c_3 i}{1 + c_4 i} e^{-\frac{I_0\tau}{1+c_3 i}} + (1 + c_3 i)(1 + c_2\Delta_i - c_2 i)(1 - e^{-\frac{I_0\tau}{1+c_3 i}}) = $$
$$= 1 + A = 1 + R = 1 + c_2\Delta_0, \tag{177}$$

from which Δ_i can be found.

For i very large, the equation becomes

$$\frac{c_3}{c_4} + (1 + c_2\Delta_i - c_2 i)I_0\tau = 1 + c_2\Delta_0 \tag{178}$$

whence

$$\Delta_i = \frac{1 + c_2\Delta_0 - \frac{c_3}{c_4}}{c_2 I_0\tau} - \frac{1}{c_2} + i \tag{179}$$

CHWEITZER's scheme retains, therefore, about the same shape as without electrotonus, at least if $\frac{c_2}{c_1} < 1 + A$.

Break-excitation is only possible if

$$\frac{1 + c_2\Delta_0 - \frac{c_3}{c_4}}{c_2 I_0\tau} < \frac{1}{c_2}$$

or (177)

$$1 + A < \frac{c_3}{c_4} + I_0\tau \tag{180}$$

6. Exponentially rising currents

During the H.N.Z. the equation of metabolism remains for the cathode

$$\frac{dx_1(t)}{dt} = - I_0 x_1(t) + I_0 \left\{ 1 + c_2 i(1 - e^{-\frac{t}{a}}) \right\} \qquad o < t < \tau \tag{181}$$

Subsequently, during the accommodation-period

$$\frac{dx_2(t)}{dt} = - I_0 \left\{ 1 + c_1 i(1 - e^{-\frac{t-\tau}{a}}) \right\} x_2(t) + I_0 \left\{ 1 + c_2 i(1 - e^{-\frac{t}{a}}) \right\} \tau < t \tag{182}$$

obtains.

The solutions will of course become even more involved than in the

case when there was no Physiological Electrotonus. The course retains the same characteristics however with this difference, that finally it does not decrease to 1 but to $\frac{1+c_2 i}{1+c_1 i}$.

For a given value of a, the threshold-value i can again be obtained at which the critical amplitude A is just reached and excitation occurs. If this happens after the utilization-time τ, it can again be proved that, on condition that $\frac{c_1}{c_2}(1+A) > 1$ *, for increasing a, t_1 has a limit t_∞ and a minimal current-gradient exists, below which no excitation can occur, however great i may become. The demonstration, which proceeds exactly as in the case without electrotonus is left to the reader.

Putting $\mu = \lim\limits_{a \to \infty} \frac{c_2 i}{a}$, then again $\mu = \frac{R}{\lambda}$, in which λ is the experimentally measured magnitude which has the same value as HILL's time-constant for accommodation.

The relations between λ, τ, A, and t_∞ can easily be discovered from the equation for $x_2(t)$.

Excitation occurs if the maximum of $x_2(t)$ is reached for $t = t_1$, and this maximum is then exactly equal to $1 + A$.

From $\frac{dx_2(t)}{dt} = o$ it follows that

$$\left\{1 + c_1 i \left(1 - e^{-\frac{t-\tau}{a}}\right)\right\}(1 + A) = 1 + c_2 i\left(1 - e^{-\frac{t_1}{a}}\right) \qquad (183)$$

For a very large this will become

$$\left\{1 + \frac{c_1 i(t_1 - \tau)}{a}\right\}(1 + A) = 1 + \frac{c_2 i t_1}{a} \qquad (184)$$

---

* This is the same condition as in the preceding section, because, if $\frac{c_2}{c_1} > 1 + A$, even after creeping up with the slightest gradient, for sufficiently large t the critical amplitude would always be exceeded and a tetanic contraction would occur. In that case no minimal gradient exists.

These cases actually present themselves, although for other organs. Consequently no accommodation is then possible.

It is interesting that the existing theories cannot provide an explanation for these phenomena (Compare SCHAEFER, p. 171).

Since it can be proved, that t_1 has a limit and consequently $\frac{i}{a}$ also, it follows that

$$\left\{1 + \frac{c_1}{c_2}\mu(t_\infty - \tau)\right\}(1 + A) = 1 + \mu t_\infty$$

whence

$$\mu = \frac{c_2 A}{c_2 t_\infty - c_1(1 + A)(t_\infty - \tau)} \tag{185}$$

Now

$$A = R \text{ and } \mu = \frac{R}{\lambda}.$$

so

$$\lambda = t_\infty - \frac{c_1}{c_2}(1 + A)(t_\infty - \tau)$$

or

$$\lambda = \tau + \left\{1 - \frac{c_1}{c_2}(1 + A)\right\}(t_\infty - \tau) \tag{186}$$

in which $1 - \frac{c_1}{c_2}(1 + A) < 0$ (condition for the existence of $\lim\limits_{a \to \infty} t_1 = t_\infty$). Hence it follows that $\lambda < \tau$.

Experimentally however we always have $\lambda > \tau$.

III

THE CASE $\tau_1 < \tau_2$

Supposing that, in the application of the general equation of metabolism to the excitation-phenomena the of nerve, $\tau_1 < \tau_2$, we must assume that the dissimilation of a certain biogenic matter X, the concentration of which is responsible for the generation of a reaction-wave, precedes the assimilation. In this case too, a picture arises which is rather attractive.

Supposing that in this case also the $K^{\cdot}$ and $Ca^{\cdot\cdot}$ ions regulate the destruction and rebuilding respectively, it is likely that $K^{\cdot}$ ions evoke the dissimilation, $Ca^{\cdot\cdot}$ ions the assimilation of the matter X.

Excitation occurs when the biogenic matter has been destroyed till the relative concentration has reached a critical value. As will be shown later on, in the case where Physiological Electrotonus plays a part, at the cathode a lower concentration of X will permanently exist, at the anode a higher one, if a subliminal current continues to flow sufficiently long. As a matter of fact, microscopic observation has shown that at the cathode the structure of the nerve becomes looser, at the anode denser.

It is furthermore known that potassium causes such a loosening of the structure, attended with dilation, while calcium has the opposite effect. The acetylcholine acquires the significance of a secondary product, which, of course, can continue its function. It has only to be assumed that the acetylcholine can start its work, as soon as the concentration of the unknown matter, which might be the lecithin for instance, has fallen to a certain critical value.

LOEB thought that the reaction-wave came into being, if the balance between the relative concentrations of the $K^{\cdot}$ and $Ca^{\cdot\cdot}$ ions was considerably disturbed. He did not assume, however, the existence of a certain excitatory matter which has to reach a critical concentration, but thought that for excitation the quotient $\frac{[K^{\cdot}]}{[Ca^{\cdot\cdot}]}$ must have a certain critical value, which is a different hypothesis.

RASHEVSKY, in as far as he adopts a physical idea at all, departs from LOEB's suppositions.

So it might be assumed that the $K^{\cdot}$ ion-concentration is propor-

tional to $I(t)$ and the $Ca^{\cdot\cdot}$ ion-concentration to $L(t)$. I want to point out again emphatically however, that, just as in the case $\tau_1 > \tau_2$ the above-mentioned reflections about $K^{\cdot}$, $Ca^{\cdot\cdot}$ and lecithin are in no way essential and only serve to make matters clearer.

Since τ_1 is also very small with regard to τ_2, τ_1 can with negligible inaccuracy be disregarded altogether and τ_2 may without more ado be called τ. It will now also be assumed, that with a fresh preparation and with sufficient preparatory treatment the concentration of the reserves, with which X is synthezised, will remain constant during the experiment.

Finally, the first case to be treated is the one in which there will be no electrotonic complications.

Then the general equation of metabolism runs as follows

$$\frac{d\xi(t)}{dt} = -I(t)\xi(t) + L(t-\tau)\varrho_0 \qquad (187)$$

In the resting state before the experiment $I(t) = I_0$ and $L(t) = L_0$, while the concentration of X at any point of the nerve is ξ_0. If by a constant current from A → K at the cathode $I(t) > I_0$, at first a diminishing of the concentration of X ensues. If the critical concentration is reached, excitation originates. This critical concentration should in any case be reached at the latest after τ sec. Subsequently the accommodation-phase will set in; in other words $L(t-\tau)$ suddenly acquires a higher value and the concentration of X recommences to rise. τ again has the significance of the H.N.Z. (in general $\tau_2 - \tau_1$).

a. Electrotonic complications will not occur $(c_1 = c_2, c_3 = c_4)$

1. The reduced equations

The general equation (187) again reduces to

$$\frac{d\xi(t)}{dt} = -I(t)\xi(t) + I(t-\tau)\xi_0$$

or to

$$\frac{dx(t)}{dt} = -I(t)x(t) + I(t-\tau) \qquad (188)$$

on condition that $x(t)$ represents the relative concentration of X to that of the resting state.

In the resting state $I(t) = I_0$ obtains and the Relative Concentration of X is everywhere 1. If a direct current is sent through AK, at the cathode

$$I(t) = I_0(1 + ci) \text{ approximately}$$

and at the anode

$$I'(t) = \frac{I_0}{1 + c'i} \qquad (189)$$

Let the critical Relative Concentration of X be $1 - A$ and the critical amplitude A.

2. Constant direct current of short duration

The general equation breaks up into the following equations

$$\left.\begin{aligned}
\frac{dx_1(t)}{dt} &= -I_0(1 + I)x_1(t) + I_0 && o < t < T \\
\frac{dx_2(t)}{dt} &= -I_0x_2(t) + I_0 && T < t < \tau \\
\frac{dx_3(t)}{dt} &= -I_0x_3(t) + I_0(1 + I) && \tau < t < \tau + T \\
\frac{dx_4(t)}{dt} &= -I_0x_4(t) + I_0 && \tau < T < t
\end{aligned}\right\} \qquad (190)$$

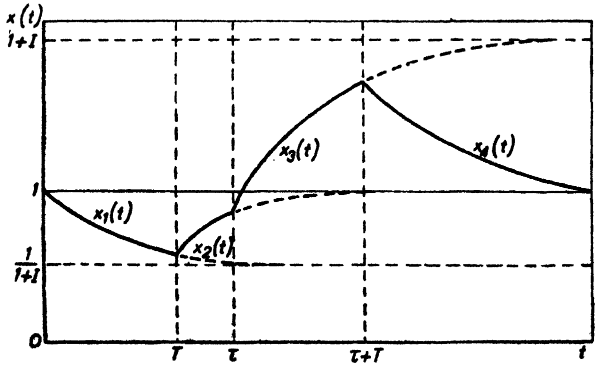


FIG. 19 – Course of the Rel. Conc. of X at the cathode with a constant current of finite duration ($\tau_1 < \tau_2$, $\tau_1 = 0$).

in which again

$$\left.\begin{aligned} x_1(o) &= 1 \\ x_1(T) &= x_2(T) \\ x_2(\tau) &= x_3(\tau) \\ x_3(\tau + T) &= x_4(\tau + T) \end{aligned}\right\} \quad (191)$$

The solutions of these equations are as follows

$$\left.\begin{aligned} x_1(t) &= \frac{1 + Ie^{-I_0(1+I)t}}{1+I} && o < t < T \\ x_2(t) &= e^{-I_0(t-T)}x_1(T) + 1 - e^{-I_0(t-T)} && T < t < \tau \\ x_3(t) &= e^{-I_0(t-\tau)}x_1(\tau) + (1 + I)\{1 - e^{-I_0(t-\tau)}\} && \tau < t < \tau + T \\ x_4(t) &= e^{-I_0(t-\tau-T)}x_3(\tau + T) + 1 - e^{-I_0(1-\tau-T)} && \tau < T < t \end{aligned}\right\} \quad (192)$$

By these functions the course of $x(t)$ is determined. After an initial fall until $t = T$ an exponential rise until $t = \tau$ originates. Then a rapid increase to above the resting value 1 until $t = \tau + T$ and subsequently an exponential decrease to the resting value 1 (Fig. 19). At moderate distances from the cathode, similar diphasic waves with smaller amplitudes originate as a result of a smaller value of c.

For the anode a similar set of equations obtains. Here approximately

$$I(t) = \frac{I_0}{1 + c'i} = \frac{I_0}{1 + I}$$

The result is a similar diphasic course with opposite and smaller amplitudes.

Between A and K there is a point where the Relative Concentration of X does not change.

3. Constant current of infinitely long duration, which does not excite

If through AK a constant current of infinitely long duration is passed, which does not excite, the first equation is

$$\left.\begin{aligned} &\frac{dx_1(t)}{dt} = -I_0(1+I)x_1(t) + I_0 \qquad o < t < \tau \\ &\text{with the solution} \\ &x_1(t) = \frac{1 + Ie^{-I_0(1+I)t}}{1+I} \end{aligned}\right\} \quad (193)$$

Subsequently however,

$$\left.\begin{aligned} &\frac{dx_2(t)}{dt} = -I_0(1+I)x_2(t) + I_0(1+I) \qquad \tau < t \\ &\text{with the solution} \\ &x_2(t) = e^{-I_0(1+I)(t-\tau)}x_1(\tau) + 1 - e^{-I_0(1+I)(t-\tau)} \\ &\quad = 1 + \frac{I}{1+I}e^{-I_0(1+I)\tau}\left\{1 - e^{-I_0(1+I)\tau}\right\} \end{aligned}\right\} \quad (194)$$

Putting $1 - x(t) = A(t)$, we obtain

$$\left.\begin{aligned} &A_1(t) = \frac{I}{1+I}\left\{1 - e^{-I_0(1+I)t}\right\} \qquad o < t < \tau \\ &\text{and} \\ &A_2(t) = A_1(\tau)e^{-I_0(1+I)t} \qquad \tau < t \end{aligned}\right\} \quad (195)$$

Hence, $x_1(t)$ falls to $x_1(\tau)$ until $t = \tau$. Then $x_2(t)$ rises again exponentially to 1 (Fig. 20).

At the other points of the nerve a similar thing happens (at and near the anode of course with the opposite amplitude).

If we wait long enough, the Relative Concentration of X for all points of the nerve will become identical again with the resting-value: the nerve has accommodated itself.

In the neighbourhood of the cathode however, there is an accelerated metabolism of X and in the neighbourhood of the anode a retarded one. At the cathode

$$\left.\begin{aligned} &\frac{dx(t)}{dt} = -I_0(1+I)x(t) + I_0(1+I), \\ &\text{at the anode} \\ &\frac{dx(t)}{dt} = -\frac{I_0}{1+I'}x(t) + \frac{I_0}{1+I'} \end{aligned}\right\} \quad (196)$$

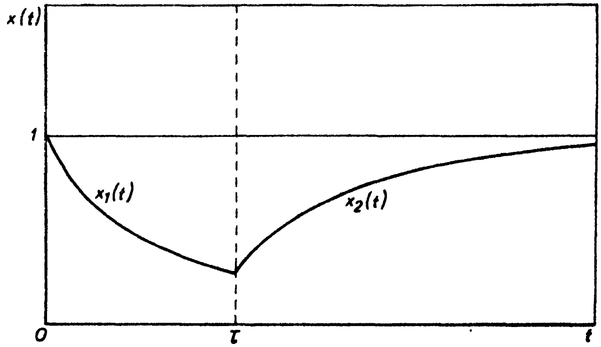


FIG. 20 – Course of the Rel. Conc. of X at the cathode with a constant current of infinitely long duration ($\tau_1 = 0$).

continuously, both with

$$x(t) = 1.$$

4. Make-excitation

If the current is sufficiently strong, so that excitation can ensue, the critical amplitude A will be reached first at the cathode, where the decrease of the Relative Concentration of X is greatest. Let the duration of the current-pulse be T, the condition for excitation is then (192)

$$\frac{I}{1+I}\left\{1 - e^{-I_0(1+I)T}\right\} = A \tag{197}$$

This is the equation for the strength-duration curve.

Although the function is quite different from the one in the case $\tau_1 > \tau_2$, the course is about the same. There is another theoretical Rheobase R_0, which would exist, if there was no accommodation viz., no change in the assimilation of X. It is discovered from $T = \infty$. So

$$\frac{R_0}{1+R_0} = A \text{ or } R_0 = \frac{A}{1-A} \tag{198}$$

The true Rheobase R however is to be determined from

$$\frac{R}{1+R}\left\{1 - e^{-I_0(1+R)\tau}\right\} = A \tag{199}$$

and it is quite possible that it is much greater than R_0. In contrast to the case $\tau_1 > \tau_2$, it is not so easy to deduce I_0 from the strength-duration curve. We ought to know three points with certainty for that purpose. It appears however, that slight inaccuracies of observation may lead to important changes in all characteristic magnitudes.

Still, it is generally possible to demonstrate that in the case of the customary preparations of the frog sciatic nerve practically always $R = R_0$, provided use is made of the property (which has been demonstrated particularly by LAPICQUE), that the chronaxie has a value of the order of 0.1 of the H.N.Z. *i.e.* 0.1 τ.

The theoretical chronaxie $t_{c,o}$, based on the theoretical Rheobase R_0, is obtained from

$$\frac{2R_0}{1+2R_0}\left\{1-e^{-I_0(1+2R_0)t_{c,o}}\right\} = A = \frac{R_0}{1+R_0} \tag{200}$$

So

$$t_{c,o} = \frac{\log 2(1+R_0)}{I_0(1+2R_0)} \tag{201}$$

The true, measured chronaxie t_c must be obtained from

$$\frac{2R}{1+2R}\left\{1-e^{-I_0(1+2R)t_c}\right\} = \frac{R}{1+R}\left\{1-e^{-I_0(1+R)\tau}\right\}$$

or

$$\frac{1-e^{-I_0(1+2R)t_c}}{1-e^{-I_0(1+R)\tau}} = \frac{1+2R}{2(1+R)} \tag{202}$$

Adopting as the average values $t_c \doteq 0.3\,\sigma$ and $\tau = 3\,\sigma$, we obtain

$$\frac{1-e^{-0,3I_0(1+2R)}}{1-e^{-3I_0(1+R)}} = \frac{1+2R}{2(1+R)}$$

It then appears, because of $R > o$, that I_0 has an upper limit, viz., 2.3 for $R = o$. For increasing R, I_0 decreases.

I_0	2.3	1.55	1.2	0.5	0.09
R	0	1	2	10	100

In all these cases $e^{-I_0(1+R)\tau} = e^{-3I_0(1+R)}$ appears negligible and we may state, that for the sciatic nerve of the frog

$$1 - e^{-I_0(1+2R)t_c} = \frac{1 + 2R}{2(1 + R)}$$

or

$$e^{-t_c I_0(1+2R)} = \frac{1}{2(1 + R)}$$

or

$$t_c = \frac{\log 2\,(1 + R)}{I_0(1 + 2R)} \tag{203}$$

Since $e^{-I_0(1+R)\tau}$ is negligible, it follows that $\frac{R}{1+R} = A$.

Hence

$$R = \frac{A}{1 - A} = R_0.$$

and the theoretical and the true chronaxie are also practically equal.

Although the theoretical and true Rheobase are practically equal, nothing can be told about the magnitude of I_0 as in the case of $\tau_1 > \tau_2$.

In the case where I, within the experimental interval, has a value which is small compared to 1, the equation for the strength-duration curve would reduce to

$$I \left\{1 - e^{-I_0 T}\right\} = A$$

or

$$\frac{I}{R} = \frac{1}{1 - e^{-I_0 T}} \tag{204}$$

Exactly the same equation is then found as in the case $\tau_1 > \tau_2$. Since $R_0 = A$ approximately and since the exact calculation would produce $R_0 = \frac{A}{1 - A}$, it may be concluded that both A and R would be small in comparison with 1.

The fact that equation (204), which is the same as for the case $\tau_1 > \tau_2$, describes the strength-duration curve so well in so many experiments, might favour the assumption that the magnitudes I and R are indeed very small in relation to 1.

Still there are, as BLAIR has observed, a number of cases in which

formula (204) does not suffice. That is why he substitued for this equation

$$\frac{I}{R} = \frac{1}{1 - \beta e^{-I_0 T}} \tag{205}$$

in which, however, the coefficient β has no physical meaning at all, and the Constant Quantity Relation is not satisfied either. It is therefore possible, that in these cases the unreduced equation (197) suffices. This result would simultaneously give the preference to case $\tau_1 < \tau_2$ over the first case $\tau_1 > \tau_2$.

For T very small, and consequently for I very large, approximation must not be used of course. Since now 1 is negligible compared to I (197) will become

$$1 - e^{-_0IT} = A$$

whence

$$IT = -\frac{1}{I_0}\log(1 - A)$$

or

$$Q_0 = iT = -\frac{1}{cI_0}\log(1 - A) \tag{206}$$

Hence here also the Constant Quantity Relation is satisfied. If A is small in comparison with 1, it follows that $Q_0 = \frac{A}{cI_0}$ which is the same formula again as for the case $\tau_1 > \tau_2$.

5. Condenser-discharge

For the condenser-discharge with initial voltage $\boldsymbol{E}$, resistance $\boldsymbol{R}$ and capacity $\boldsymbol{C}$ we have again $i = \frac{\boldsymbol{E}}{\boldsymbol{R}} e^{-\frac{t}{\boldsymbol{RC}}}$

Putting $a = \frac{1}{\boldsymbol{RC}}$ and $I = \frac{c\boldsymbol{E}}{\boldsymbol{R}}$, the equation of metabolism at the cathode for $o < t < \tau$ becomes

$$\frac{dx_1(t)}{dt} = -I_0(1 + Ie^{-at})\,x_1(t) + I_0 \tag{207}$$

and has the solution

$$x_1(t) = I_0 e^{-I_0(t-\frac{I}{a}e^{-at})} \int_0^t e^{I_0(u-\frac{I}{a}e^{-au})} du + e^{-I_0\left\{t+\frac{I}{a}(1-e^{-at})\right\}} \tag{208}$$

For $t > \tau$ the equation

$$\frac{dx_2(t)}{dt} = - I_0 \left\{1 + Ie^{-at}\right\} x_2(t) + I_0\left\{ 1 + Ie^{-a(t-\tau)}\right\} \text{ holds} \tag{209}$$

If no excitation occurs, the course of $x(t)$ is a diphasic wave (Fig. 21). The function $x_1(t)$ has in general a minimum. When this minimum

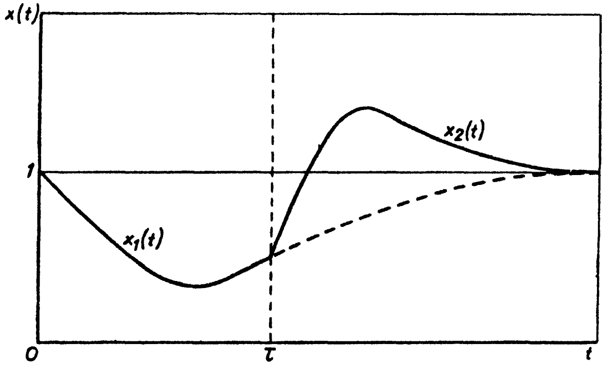


FIG. 21 – Course of the Rel. Conc. of X at the cathode after a condenser-discharge ($\tau_1 = 0$).

is reached at a time $t_1 < \tau$, threshold-excitation will occur, if at this moment also the minimum is exactly equal to $1 - A$.

From (207) it follows, if we put $\frac{dx_1(t)}{dt} = o$,

$$I_0(1 + Ie^{-at_1})(1 - A) = I_0$$

or

$$Ie^{-at_1} = \frac{A}{1-A} = R_0 \tag{210}$$

At the same time, because of $x_1(t_1) = 1-A$,

$$I_0 e^{-I_0(t_1-\frac{I}{a}e^{-at_1})} \int_0^{t_1} e^{I_0(u-\frac{I}{a}e^{-au})} du + e^{-I_0\left\{t_1+\frac{I}{a}(1-e^{-at_1})\right\}} = 1 - A \tag{211}$$

In order to obtain the Volt-Capacity curve, t_1 should be eliminated from (210) and (211).

From (210) it follows that

$$e^{-at_1} = \frac{R_0}{I} \text{ and } e^{-I_0 t_1} = \left(\frac{R_0}{I}\right)^{\frac{I_0}{a}} \qquad \text{while} \qquad t_1 = \frac{1}{a} \log \frac{I}{R_0} \tag{212}$$

We then obtain

$$I_0 \left(\frac{R_0}{I}\right)^{\frac{I_0}{a}} e^{\frac{I_0 R_0}{a}} \int_0^{\frac{1}{a}\log\frac{I}{R_0}} e^{I_0\left(u - \frac{I}{a} e^{-au}\right)} du + \left(\frac{R_0}{I}\right)^{\frac{I_0}{a}} e^{-\frac{I_0}{a}(I-R_0)} =$$

$$= 1 - A = \frac{1}{1+R_0} \tag{213}$$

Putting $e^{-au} = z$, we find that

$$\frac{I_0}{a}\left(\frac{R_0}{I}\right)^{\frac{I_0}{a}} e^{\frac{I_0 R_0}{a}} \int_{\frac{R_0}{I}}^{1} \frac{e^{-\frac{I_0 I}{a} z}}{z^{\frac{I_0}{a}+1}} dz + \left(\frac{R_0}{I}\right)^{\frac{I_0}{a}} e^{-\frac{I_0}{a}(I-R_0)} = \frac{1}{1+R_0} \tag{214}$$

This exact equation for the Volt-Capacity curve (written $I = \frac{c\boldsymbol{E}}{\boldsymbol{R}}$ and $R_0 = \frac{c\boldsymbol{E}_0}{\boldsymbol{R}}$) cannot be reduced any further, because the integral is not elementary.

We now ask ourselves what will become of the quotient of chronaxie and RC for twice the Rheobasic tension, in other words of at_c. For twice the Rheobasic tension $I = 2\,R_0$.

Putting $\frac{I_0}{a} = p$, equation (214) becomes

$$\frac{p e^{pR_0}}{2^p} \int_{\frac{1}{2}} \frac{e^{-2pR_0 z}}{z^{p+1}} dz + \frac{e^{-pR_0}}{2^p} = \frac{1}{1+R_0} \tag{215}$$

By one partial integration (215) becomes

$$pe^{pR_0}\int_{\frac{1}{2}}^{1}\frac{e^{-2pR_0z}}{z^p}\,dz = \frac{2^{p-1}}{1+R_0} \tag{216}$$

For the theoretical chronaxie we obtained previously

$$t_c = \frac{\log 2(1+R_0)}{I_0(1+2R_0)}$$

whence

$$I_0t_c = \frac{\log 2(1+R_0)}{1+2R_0} \tag{217}$$

and we have to examine $at_c = \dfrac{I_0t_c}{p}$.

We should therefore deduce p from (216), which is not very easy, in view of the intricacy of this transcendental equation.

We may ask ourselves how far $at_c = \frac{1}{2}\log 2 = 0.347$ still obtains exactly or at least holds approximately. In this case

$$p = \frac{2}{1+2R_0}\,\frac{\log 2(1+R_0)}{\log 2} \tag{218}$$

would have to be a root of equation (216).

To Dr C. J. Bouwkamp of Eindhoven, I owe the answer to this question. He succeeded in solving numerically equation (216) and he found that although p is in general not exactly equal to $\dfrac{2}{1+2R_0}\,\dfrac{\log(1+R_0)}{\log 2}$ (except for $p = 2$, $R_0 = 0$), this function is an excellent approximation. I may be allowed to omit the extensive discussion but I propose to compare a few numerical results in a table.

Let p_1 be the exact value of p for several values of R_0, calculated from (216) and let p_2 be the value calculated from approximation (218). The exact value of at_c will then be $\dfrac{p_2}{p_1} \times \frac{1}{2}\log 2$.

We now obtain:

R_0	p_1	p_2	at_c (exact)
0	2	2	0.347
0.69	1.45	1.48	0.354
2.02	0.99	1.03	0.361
4.76	0.63	0.67	0.369
10.8	0.37	0.40	0.375
24.2	0.21	0.23	0.380

This shows how all these values remain in the neighbourhood of the value 0.37, found by LAPICQUE to be the average, however the values of R_0 may differ.

The evidence that for a condenser-discharge the Constant Quantity Relation exists, does not produce important difficulties. Since the charge Q, which passes through the nerve until excitation occurs, is

$$Q = \frac{E}{aR}(1 - e^{-at_1})$$

we obtain

$$Q = \frac{I}{ca}\left(1 - \frac{R_0}{I}\right). \tag{219}$$

For I very large, therefore

$$Q_0 = \lim_{I \to \infty} \frac{I}{ca}.$$

In equation (214)

$$\lim_{I \to \infty} \left(\frac{R_0}{I}\right)^{\frac{I_0}{a}} = \lim \left\{\left(\frac{R_0}{I}\right)^{\frac{R_0}{I}}\right\}^{\frac{I_0 I}{R_0 a}} = 1. \tag{220}$$

Since $\lim\limits_{a \to \infty} e^{\frac{I_0 R_0}{a}} = 1$, and the integral for increasing I remains also finite, the first term of (214) tends to zero.

The second term tends to $e^{-\frac{I_0 I}{a}}$.

So equation (214) reduces to

$$e^{-\frac{I_0 I}{a}} = 1 - A \quad \text{or} \quad \frac{I}{a} = -\frac{lg(1-A)}{I_0}$$

and

$$Q_0 = -\frac{lg(1-A)}{cI_0} \tag{221}$$

which is the same value as for rectangular current-pulses.

6. The other cases

Having discussed some of the most important cases and having found that the formula, although a little more complicated, sufficed to describe the phenomena just as well as those resulting from the assumption $\tau_1 > \tau_2$, we may leave the calculation of the formulae of the other cases to the reader and only communicate the most important results.

With exponentially and linearly rising currents one finds again that for decreasing gradient the "Nutzzeit" increases. Again there is a minimal gradient and in this case the Nutzzeit has reached a certain limit t_1. The relation between the reversal of this minimal current gradient (HILL's λ), the relaxation-time τ, the maximal Nutzzeit t_∞ and the critical amplitude A is now found as

$$\lambda = \tau - At_\infty \tag{222}$$

Again it follows that $\lambda < \tau$, which is not in accordance with the experiments. As was stated earlier, with the case $\tau_1 > \tau_2$, the correction of some of the proposed hypotheses in Chapter IV will smooth away this quantitative difficulty for this case as well.

In case of "break-excitation" and of a gap in a constant current we find qualitatively the same results with a slightly different formula. For A small, they all reduce to those of the case $\tau_1 > \tau_2$. For alternating currents we find again that

$$\frac{I}{R} = \pi nk \tag{223}$$

the relation, experimentally discovered by KATZ and diverging from the one predicted by HILL.

7. Excitability

As for the excitability at a given point N of the nerve, we again define $P = \frac{1}{Q}$, in which Q is the electrical charge which, during a current-pulse of very short duration, entering at a distant peripheral point M of the nerve and leaving it at N, just evokes excitation.

If at a moment t_1 the amplitude of the Relative Concentration of X at the point N is $A(t_1)$ and if we now measure the excitability by applying a very short current-pulse of strength i and duration T, which is just strong enough to excite, we find

$$iT = -\frac{1}{I_0 c} lg \frac{1 - A}{1 - A(t_1)} \tag{224}$$

If A is small compared to 1, we may reduce this formula to

$$iT = \frac{A - A(t_1)}{cI_0} \tag{225}$$

and the excitability is

$$P(t_1) = \frac{cI_0}{A - A(t_1)}, \tag{226}$$

the same formula as in the case $\tau_1 > \tau_2$.

8. Changes of the Rheobase after accommodation

Let a constant current i be sent through the nerve—if necessary after creeping-up—and after accommodation has been obtained, let a current Δ_i in the same direction be superimposed, which is just strong enough to evoke excitation. If Δ_0 is the ordinary Rheobase and if $e^{-I_0\tau}$ is, as usual, negligible, we find the same formula as in the case $\tau_1 > \tau_2$, viz.

$$\Delta_i = (1 + ci)\Delta_0 \tag{227}$$

The extra current, necessary for excitation, rises instantly linearly with the strength of the conditioning current, instead of doing so after an initial decrease to a flat minimum, as CHWEITZER's scheme demonstrates. So we find the same discrepancy with the experiment, which, however, will be abolished by the proposed correction of the equation of metabolism in Chapter IV.

b. The influence of the Physiological Electrotonus

$(c_1 > c_2, c_3 > c_4)$

1. The general equation

Taking the defined Physiological Electrotonus into account, we should start (while putting $\tau_1 = o$ and $\tau_2 = \tau$) from the equation

$$\frac{d\xi(t)}{dt} = -I(t)\xi(t) + L(t-\tau)\varrho_0$$

For a current of a given form $i(t)$ at the cathode obtains again

$$I(t) = I_0 \{1 + c_1 i(t)\}$$

and

$$L(t) = L_0 \{1 + c_2 i(t)\}$$

In this case we should use the term catelectrotonus, if $\frac{c_2}{c_1} < 1$. The general equation now reduces to

$$\frac{dx(t)}{dt} = -I_0 \{1 + c_1 i(t)\} x(t) + I_0 \{1 + c_2 i(t-\tau)\}$$

At the anode similarly obtains (228)

$$\frac{dx(t)}{dt} = -\frac{I_0}{1 + c_3 i(t)} x(t) + \frac{I_0}{1 + c_4 i(t-\tau)}.$$

There is anelectrotonus if $\frac{c_4}{c_3} < 1$.

Now, it is also possible with the help of these equations to discuss all the examined current-forms for the case in which the Physiological Electrotonus does play a part.

2. Cases in which the Physiological Electrotonus has no influence

Just as in the case $\tau_1 > \tau_2$ the derived formulae, which refer to the phenomena developing within the H.N.Z., will remain the same. This holds therefore for the strength-duration curve, for constant current-pulses, for the Rheobase, for the Constant Quantity Relation, for the Volt-Capacity curve and the relation for high-frequency alternating currents. The multiplying constant c is, in this case, c_1.

3. The schemes of Pflüger and Chweitzer

With a subliminal constant current of relatively short duration $T < \tau$, the change of the Relative Concentration of X remains independent of the Physiological Electrotonus for $t \leq \tau$. Subsequently, catelectrotonus will have the effect that the rise of the Relative Concentration of X will be less strong i.e. the post-cathodal depression decreases. For t sufficiently large, the Relative Concentration of X tends again to the resting-value 1.

However, for a constant current of infinitely long duration the Relative Concentration of X will, after an initial fall, gradually increase to a value $\frac{1 + c_2 i}{1 + c_1 i} < 1$.

The influence of the catelectrotonus is therefore such, that the excitability at the cathode is enhanced.

At the anode there are oppositely-directed changes. Here, with an infinitely long duration of the current, the Relative Concentration of X tends to $\frac{1 + c_3 i}{1 + c_4 i} > 1$.

The anelectrotonus therefore causes a decrease of excitability here. Just as in the case $\tau_1 > \tau_2$ a (partial) explanation of PFLÜGER's scheme can now be supplied.

The developments of the formulae belonging to CHWEITZER's scheme are, of course, even more involved. In this case however, curves of the same type as in the absence of Physiological Electrotonus are obtained.

In the case where the extra-current and the conditioning current have the same direction we obtain, if as usual $e^{-I_0 \tau}$ is negligible

$$\Delta_i = \Delta_0 + i\left(c_2 \Delta_0 + \frac{c_3}{c_1} - 1\right) \tag{229}$$

If $\frac{c_3}{c_1} > 1 - A$, so that even for large i no tetanic contraction can ensue, Δ_i will rise linearly with increasing i.

If $\frac{c_3}{c_1} \leq 1 - A$, Δ_i will decrease linearly until the conditioning current, even after extremely slow creeping up, evokes a tetanic contraction.

No new results of importance are therefore obtained.

IV

CRITICISM AND EXTENSION

1. The quantitative discrepancies

After the extensive discussions of the two cases $\tau_1 > \tau_2$ and $\tau_1 < \tau_2$, it will be useful to examine once more what the proposed equation to explain the excitation-phenomena has achieved and under what circumstances the results deviate from those obtained from the experiments. In the first place it appeared, that both cases provide an entirely equivalent qualitative explanation to all phenomena. It is therefore impossible to decide whether the assumption: precedence of dissimilation to assimilation of a certain excitatory matter ($\tau_1 < \tau_2$) is to be preferred to the opposite assumption ($\tau_1 > \tau_2$). The assumption that destruction is easier than construction and more so than re-construction is attractive, but merely a matter of sentiment.

Though the two cases suffice qualitatively, quantitatively there are a few results which tend to show that the proposed equation can only be a fair approximation. These divergences only appear to occur, when the accommodation plays an important part.

In the first place, the value of the magnitude λ, in HILL's theory the time-constant of the accommodation, is too small. In the cases discussed it is, as has been proved, smaller than the H.N.Z., while experimentally λ can in some cases be as large as ten times the H.N.Z. The fact that the theoretical value of λ is too small, tends to show *that the accommodation develops more gradually after the H.N.Z. than is postulated by the proposed equation of metabolism.*

The same conclusion regarding break-excitation can be drawn from CLUZET's, CARDOT and LAUGIER's, and SOLANDT's experiments. The Rheobase is obtained by them after an infinitely long utilization-time. As appears from equations (110) and (257) the Rheobase would be approximately reached after the H.N.Z. An experiment of SOLANDT gives, for instance,

$T\sigma$	2	4	6	8	12	16	24	32	40
i'	16	7.30	5.55	3.69	3.19	3.00	2.82	2.76	2.87

Since this experiment refers to the sciatic nerve of the frog, the Rheobase should have been reached after 2 or 3 σ, while the experiment fixes it at about 24 σ. Here also, the divergence points to a slow development of the accommodation.

The fact, that in Chapter II we put $\tau_2 = o$ and in III $\tau_1 = o$, has no important significance. It only reduces the H.N.Z. from τ to $\tau_1 - \tau_2$ and $\tau_2 - \tau_1$ respectively.

Also, the observance of the Physiological Electrotonus does not abolish the difficulties. On the contrary it appears, that some experiments, in which the Physiological Electrotonus plays a part, similarly show deviations from the theory. As was said before, CHWEITZER's theoretical scheme approaches the experimental one only, if the nerve is beforehand treated with KCl.

But even then there are divergences, for BOUMAN (1937) has determined strength-duration curves and volt-capacity curves, also of normal nerves, in the cases where catelectrotonus and anelectrotonus respectively had been evoked by a constant polarizing current and, while keeping to HILL's formulae, has determined the time-constant k.

Let i be the strength of the polarizing or conditioning current and j the strength of the superimposed current and j_0 the Rheobase, then our theory produces in case $\tau_1 > \tau_2$ for the strength-duration curve

$$\frac{j}{j_0} = \frac{1}{1 - e^{-I_0(1+c_1 i)T}} \tag{230}$$

Compared with HILL's formula the time-factor k_i would be

$$k_i = \frac{1}{I_0(1 + c_1 i)} = \frac{k_0}{1 + c_1 i} \tag{231}$$

Also the formula for the volt-capacity curve, which now becomes

$$\frac{E}{E_0} = \left\{ I_0(1 + c_1 i)RC \right\}^{\frac{1}{I_0(1+c_1 i)RC-1}} \tag{232}$$

produces the same result.

Hence we should obtain $k_i < k_0$.

BOUMAN comes to the conclusion however, that $k_i > k_0$. The latter observation also holds, if the nerve is previously treated with

KCl. It must be stated that BOUMAN's conclusions do not quite agree with earlier experiments by CARDOT and LAUGIER and with those made by KODERA, but we have to admit, that the theory, in as far it has been developed in Chapter II ($\tau_1 > \tau_2$), cannot be quite accurate. Besides, it was observed before (BLAIR), that HILL's formulae by no means always suffice.

In our treatment of the problem according to III ($\tau_1 < \tau_2$), the above-mentioned objections will only obtain, if the critical amplitude A is small, so that the formulae pass into those of thefirst case.

Finally, there is one more discrepancy between theory and experiment in RUSHTON's and KATZ's work.

2. The generalized equations

It is now possible to do away with these difficulties by correcting the equation of metabolism so far used:

$$\frac{d\xi(t)}{dt} = -I(t-\tau_1)\xi(t) + L(t-\tau_2)\varrho(t)$$

which, as was stated before, can only be an approximation.

What was being supposed, for instance, about the events at the cathode?

1⁰. Before the closing of the current the metabolizing-process of he matter X at the cathode had been determined by the equation

$$\frac{d\xi(t)}{dt} = -I_0\xi(t) + L_0\varrho(t)$$

in which I_0 and L_0 were measures of the constant concentrations of two different ions at this spot.

2⁰. If the current was closed, it was assumed that the concentrations of these ions, measured with the same measure, changed from I_0 and L_0 to $I_0(1+c_1i)$ and $L_0(1+c_2i)$ respectively; it was added however, that these new concentrations would only reveal themselves in the metabolizing-process after the respective relaxation-times τ_1 and τ_2 (Hyp. IV). I now drop this Hyp. IV and instead assume:

HYPOTHESIS IVa

The different cations accumulating at a certain spot will start to do their work of destruction and construction respectively, of the elements of X after different times varying from $t = o$ to $t = \infty$ with averag τ_1 and τ_2 respectively.

This means:

Before the closing of the current, at the cathode the dissimilating ions, in a concentration proportional to the dissimilation-coefficient I_0, will continuously do their activating work and they will continue to do so even after the closing. After the closing of the current the number of cations at the cathode will increase and, possibly dependent of the probability of encountering molecules of X, they will also share in the dissimilation-rate. In other words: of the ions which between $t = o$ and $t = \infty$ enlarge the dissimilation-coefficient from I_0 to $I_0(1 + c_1 i)$, the number of which is consequently proportional to $I_0 c_1 i$, each will take its place in the dissimilation-process with a different relaxation-time, as it were.

For the assimilating ions the same obtains.

I further assume:

HYPOTHESIS IVb

The average relaxation-time of the dissimilating ions τ_1, is, at least within generous limits, independent of ι, while the same is true for the assimilating ions.

Let $\alpha(\theta)$ be the probability of the occurrence of a certain relaxation-time θ, then

$$\int_0^\infty \alpha(\theta) d\theta = 1 \qquad (233)$$

which means, that all relaxation-times are possible.

The fact that the average relaxation-time is τ, is brought out by the relation

$$\int_0^\infty \theta\alpha(\theta) d\theta = \tau \qquad (234)$$

Let further $\alpha(\theta) = o$ and $\alpha(\infty) = o$.

Representing the equation of metabolism after the closing of the current by

$$\frac{d\xi(t)}{dt} = -I_0 \{ 1 + I(t) \} \xi(t) + L_0 \{ 1 + L(t) \} \varrho_0 \qquad (235)$$

it then follows, that during the passing of a constant current of duration T:

$$I(t) = c_1 i \int_0^t a_1(\theta)d\theta \qquad o < t < T \qquad (236)$$

For the assimilation we have correspondingly

$$L(t) = c_2 i \int_0^t a_2(\theta)d\theta \qquad o < t < T \qquad (237)$$

If the current is cut off after T sec., this cutting off may be imagined in this way, that on the original current of the strength i another of the same strength but of opposite direction is superimposed. In that case we obtain

$$I(t) = c_1 i \int_0^t a_1(\theta)d\theta - c_1 i \int_0^{t-T} a_1(\theta)d\theta = c_1 i \int_{t-T}^t a_1(\theta)d\theta \qquad (238)$$

and in the same way

$$L(t) = c_2 i \int_{t-T}^t a_2(\theta)d\theta \qquad (239)$$

If the current is variable, then during the passing of the current obtains

$$I(t) = c_1 \int_0^t i(t-\theta)a_1(\theta)d\theta \qquad o < t < T \qquad (240)$$

Subsequently

$$I(t) = c_1 \int_{t-T}^t i(t-\theta)a_1(\theta)d\theta \qquad T < t < \infty \qquad (241)$$

The distributive function of the relaxation-times is of course not quite determined by these equations; we ought to know exactly what happens in the nerve. In the distributive function of Poisson

$$a_1(\theta) = A_1 \theta^{m_1-1} e^{-n_1\theta} \qquad (242)$$

a probability-distribution is found however, which suffices excellently to describe the phenomena.

Substitution in (233) and (234) now produces

$$a_1(\theta) = \frac{n_1^{n_1\tau_1}\,\theta^{n_1\tau_1-1}\,e^{-n_1\theta}}{\Gamma(n_1\tau_1)} \tag{243}$$

Hence during the passing of a constant current

$$I(t) = c_1 i \int_0^t A_1 \theta^{m_1-1} e^{-n_1\theta}\, d\theta = c_1 i\, \frac{\Gamma_{n_1 t}(n_1\tau_1)}{\Gamma(n_1\tau_1)} = c_1 i \varphi_{n_1 t}(n_1\tau_1) \tag{244}$$

in which $\Gamma_{nt}(n\tau)$ represents the incomplete Γ function.

Furthermore $\varphi_{nt}(n\tau)$ is a function which increases sigmoidally from o to 1. In cases where there is no confusion possible we may simply write $\varphi_1(t)$ and $\varphi_2(t)$ instead of $\varphi_{n_1 t}(n_1\tau_1)$ and $\varphi_{n_2 t}(n_2\tau_2)$. What is now the difference regarding the original conception of the dissimilation-coefficient?

As long as the current did not flow, the dissimilation-coefficient was I_0. τ_1 sec. after the closing of the current, the dissimilation-coefficient suddenly jumped to the new value $I_0(1 + c_1 i)$ and kept this value for a time as long as the duration of the current. Then it jumped immediately back to I_0.

With the new treatment of the problem, immediately after the closing of the current the dissimilation-coefficient will begin to rise from $t = o$ along a sigmoidal curve to the value $I_0(1 + c_1 i)$, which is only reached after an infinitely long time.

If the current is withdrawn, the dissimilation-coefficient will decrease again to I_0 along a sigmoidal curve (Fig. 22). The form of these sigmoidal curves is determined by the constants n_1 and τ_1. The greater n_1 is, the more the development of the dissimilation-coefficient will begin to resemble the discontinuous one of the original treatment. The sigmoidal development of the assimilation-coefficient happens in the same way, with proper constants n_2 and τ_2. It should be noticed that the values of τ_1 and τ_2 have nothing to do with the numerical values in the former part, where in the first case they were $\tau_2 = o$ and $\tau_1 =$ the H.N.Z. and in the second case exactly the reverse $\tau_1 = o$ and $\tau_2 =$ the H.N.Z.

It is clear that this picture will agree much better with reality. Just after the closing of the current the ions begin to move to their new sites and gradually the new concentrations begin to form. Parallel to this the dissimilation- and assimilation-rates attain their new values. On break opposite developments take place.

It is furthermore clear that with the help of the generalized equation all the phenomena discussed can be just as well described qualitatively, while quantitatively even better agreement is obtained. On the other hand the introduction of the incomplete

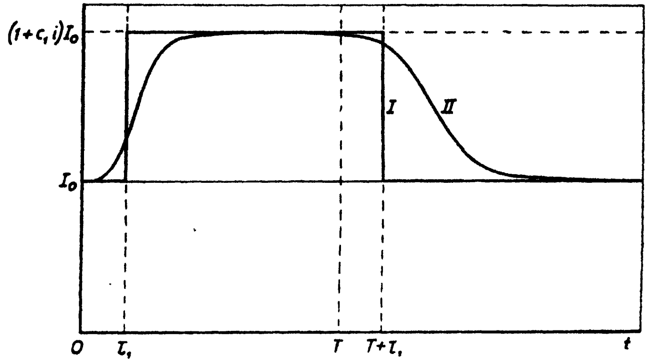


FIG. 22 – Course of the changes of the dissimilation-coefficient at the cathode with a constant current of finite duration T according to the first approximation and to the second one.

Γ functions leads of necessity to very complicated formulae, which nearly always do not admit of simple expressions. Nevertheless it can be made clear, that the generalized equation suffices better.

Finally, in this case also the dilemma remains, that we are not able to decide whether the dissimilation of the biogenic matter X develops quicker than the assimilation or the reverse.

On the assumption that the former is the case, τ_1 will be small and n_1 large. The dissimilation-coefficient remains for almost τ_1 sec. nearly I_0, in order to rise quickly to $I_0(1+c_1 i)$ afterwards. For the assimilation τ_2 is large and n_2 much smaller. The result is, that the assimilation-coefficient and accordingly also the accommodation develop much more gradually.

In the case where the assimilation of X develops quicker than the dissimilation, the relations are exactly reversed.

3. The "état d'excitation" with constant current

Passing on once again to the equation for the Relative Concentration $x(t)$ of X, we obtain for the cathode during the passing of the current

$$\frac{dx_1(t)}{dt} = -I_0 \left\{ 1 + c_1 i\varphi_1(t) \right\} x_1(t) + I_0 \left\{ 1 + c_2 i\varphi_2(t) \right\} \quad \ldots . o < t < T \tag{245}$$

After the current has been cut off

$$\frac{dx_2(t)}{dt} = -I_0 \left[1 + c_1 i \left\{ \varphi_1(t) - \varphi_1(t-T) \right\} \right] x_2(t) +$$
$$+ I_0 \left[1 + c_2 i \left\{ \varphi_2(t) - \varphi_2(t-T) \right\} \right] \ldots . T < t < \infty \tag{246}$$

At the anode, the equations become approximately

$$\frac{dx_1(t)}{dt} = -\frac{I_0}{1 + c_3 i\varphi_3(t)} x_1(t) + \frac{I_0}{1 + c_4 i\varphi_4(t)} \ldots . o < t < T \tag{247}$$

$$\frac{dx_2(t)}{dt} = -\frac{I_0}{1 + c_3 i \left\{ \varphi_3(t) - \varphi_3(t-T) \right\}} x_2(t) + \frac{I_0}{1 + c_4 i \left\{ \varphi_4(t) - \varphi_4(t-T) \right\}} \quad \ldots . T < t < \infty \tag{248}$$

In view of the impossibility of arriving at simple formulae, I confine myself to the phenomena at the cathode.

The equations comprise, dependent on the values of n_1, τ_1, n_2 and τ_2, the two cases when $x_1(t)$ at first begins to rise or to drop.

If n_1, for instance, is large and τ_1 small, while n_2 is small and τ_2 large, we find, that the current at first decreases the Relative Concentration of X, in other words, that the dissimilation develops before the assimilation.

The solution of the first equation (245) runs as follows (if we put $c_1 i = I_1$ and $c_2 i = I_2$):

$$e^{\int_0^t I_0 \{1 + I_1\varphi_1(u)\} du} x_1(t) = 1 + I_0 \int_0^t \left\{ 1 + I_2\varphi_2(u) \right\} e^{\int_0^u I_0 \{1 + I_1\varphi_1(v)\} dv} du \quad . . o < t < T \tag{249}$$

This equation can only slightly be simplified. Because of

$$\int_0^t \varphi_{n_1u}(n_1\tau_1)du = t\varphi_{n_1t}(n_1\tau_1) - \tau_1\varphi_{n_1t}(n_1\tau_1 + 1) \tag{250}$$

we obtain, remembering $\varphi_1(u) = \varphi_{n_1u}(n_1\tau_1)$ etc.,

$$e^{I_0t[1+I\{\varphi_{n_1t}(n_1\tau_1) - \frac{\tau_1}{t}\varphi_{n_1t}(n_1\tau_1+1)\}]}x_1(t) =$$

$$1 + I_0\int_0^t \{1 + I\varphi_{n_2u}(n_2\tau_2)\}\, e^{I_0u[1+I\{\varphi_{n_1u}(n_1\tau_1) - \frac{\tau_1}{u}\varphi_{n_1u}(n_1\tau_1+1)\}]}du \tag{251}$$

In the case where $\left.\begin{matrix} n_1 \text{ large, } \tau_1 \text{ small} \\ n_2 \text{ small, } \tau_2 \text{ large} \end{matrix}\right\}$ and $T = \infty$ i.e., with a constant current of infinitely long duration, $x_1(t)$ will at first begin to decrease very slowly $\left(\frac{dx_1(t)}{dt}_{t=o} = o\right)$ and afterwards quicker. Then a minimum is reached at a time t_1 which is obtained from $\frac{dx_1(t)}{dt} = o$ and at which the état d'excitation or local excitatory disturbance is maximal. After this minimum has been reached, $x_1(t)$ returns gradually to the original resting-value 1 if there is no Physiological Electrotonus ($c_1 = c_2$), otherwise to the new level $\frac{1+c_2i}{1+c_1i} < 1$, ($c_2 < c_1$) (Fig. 23).

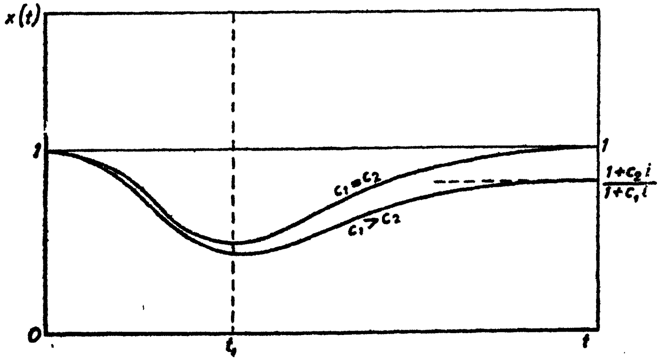


FIG. 23 – Course of the Rel. Conc. of X at the cathode with a constant current of infinitely long duration. – If $c_1 > c_2$, stabilization ensues at a new level. (Dissimilation develops before assimilation).

It is impossible to express the time t_1 explicitly. On the other hand we may state, that this time, at which the local excitatory disturbance is maximal, is in general not exactly equal to the H.N.Z. For subliminal currents it is larger, for supraliminal currents it would be smaller than the H.N.Z., but in this last case excitation would have occurred already earlier of course.

For the H.N.Z. T_H we have the Rheobase Δ and $x_1(T_H) = 1 - A$, while $\frac{dx_1(t)}{dt} = o$.

From (241) it follows that

$$\left\{ 1 + c_1 \Delta \varphi_1(T_H) \right\} (1-A) = 1 + c_2 \Delta \varphi_2(T_H)$$

or

$$\Delta = \frac{A}{(1-A)\; c_1 \varphi_1(T_H) - c_2 \varphi_2(T_H)} \tag{252}$$

This equation therefore produces the relation between Rheobase and H.N.Z.

From this relationship it is directly clear, that the Rheobase can be appreciably greater than was found before, when $R = c_1 \Delta = \frac{A}{1-A}$, for $\varphi_1(T_H) < 1$ and $\varphi_2(T_H) > o$.

Hence $\Delta > \frac{A}{c_1(1-A)}$.

If the constant current has a finite duration T, then $x_1(t)$ at first decreases to the value $x_1(T)$. Afterwards equation (246) is to be used, which has the solution

$$e^{\int_T^t I_0 [1 + I_1 \{\varphi_1(u) - \varphi_1(u-T)\}]\, du}\; x_2(t) = x_1(T) +$$

$$+ I_0 \int_T^t \left[1 + I_2 \left\{ \varphi_2(u) - \varphi_2(u-T) \right\} \right] e^{\int_T^u I_0 [1 + I_0 \{\varphi_1(v) - \varphi_1(v-T)\}]\, dv}\, du \;\ldots\; T < t < \infty \tag{253}$$

At the point $t = T$ the connecting curves have the same tangent. $x_2(t)$, therefore, at first still decreases for $T < t_1$, reaches a minimum for $t_2 < t_1$, in order to rise rapidly till beyond the resting-value 1 at

least if c_2 is large enough, it reaches a maximum and decreases again slowly to 1 (Fig. 24). As before, we find a diphasic course.

If c_2 is small enough, the rapid rise after the reaching of the minimum at the time $t = t_2$ will not lead to a crossing of the normal

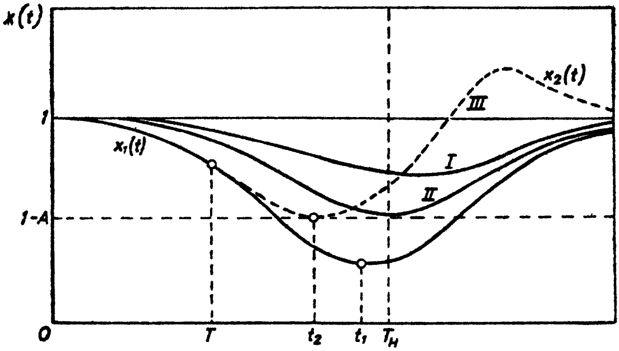


FIG. 24 – Course of the Rel. Conc. of X at the cathode with a constant current of
1. infinitely long duration, I (subliminal)
2. infinitely long duration, II (Rheobase)
3. finite duration, III (threshold value)
$c_1 = c_2$,

level, so in that case the curve becomes mono-phasic (Fig. 25), and there will not be any post-cathodal depression.

Excitation for threshold-value will occur, if at the moment $t = t_2$, when the état d'excitation is maximal, $x_2(t) = 1 - A$ also.

So we must have

$$\frac{dx_2(t)}{dt} = 0$$

or

$$[1 + I_1 \{\varphi_1(t) - \varphi_1(t-T)\}]\,(1-A) = 1 + I_2 \{\varphi_2(t) - \varphi_2(t-T)\} \quad (254)$$

and

$$x_2(t) = 1-A$$

or

$$e^{\int_T^t I_0[1+I_1\{\varphi_1(u) - \varphi_1(u-T)\}]du}\,(1-A) = x_1(T) +$$

$$+ I_0 \int_T^t [1 + I_2 \{\varphi_2(u) - \varphi_2(u-T)\}]\, e^{\int_T^u I_0[1+I_1\{\varphi_1(v) - \varphi(v-T)\}]dv}\, du \quad (255)$$

If t is eliminated from these two equations a relationship

$$F(i,T) = 0 \qquad (256)$$

originates, which represents the strength-duration curve.

For very small durations of time and consequently very high intensities the curve will behave like a hyperbola. If T increases, i becomes smaller, till the curve reaches a minimum for $T = T_H$ and in that case the intensity is equal to the Rheobase. The further

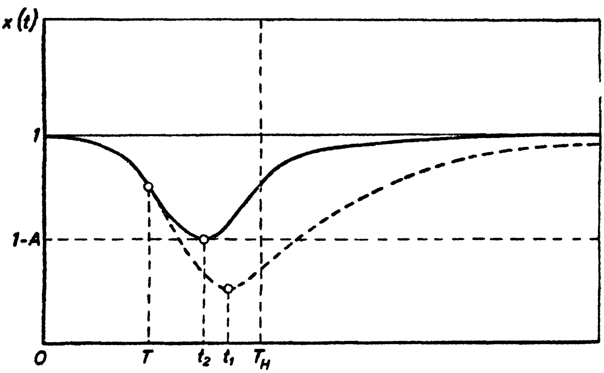


FIG. 25 – Course of the Rel. Conc. of X at the cathode with a constant current of finite duration, but for the case $c_2 \ll c_1$.

part of the curve is of no importance to the experiments and so the first part ($0 < T < T_H$) has the same form as those previously obtained. It will be clear that in many cases it will be possible to describe its form by HILL's formula.

As can be seen once more from Fig. 25, the time t_2 at which the critical amplitude is reached and excitation occurs, is later than the moment of breaking the current. I would call this the "Critical Time". Only for the Rheobase is this Critical Time equal to the duration of the current and also equal to the H.N.Z.

So it may be possible to prevent excitation even after a super-threshold current-pulse by the application of a second strong current-pulse in the opposite direction, immediately after the first. This phenomenon, which has frequently been observed (RUSHTON, KATZ), could only be explained by RUSHTON's theory. It follows from our generalized formula only, not from the first simplified ones.

If the assimilation of X should develop quicker by the current than the dissimilation, then we can use the same formulae, provided $-A$ is substituted for A.

4. The Constant Quantity Relation

Although the generalized equation produces insurmountable difficulties, yet some important conclusions may be drawn. One of them refers to the Constant Quantity Relation viz. to

$$\lim_{T \to 0} iT = D_0$$

Writing (254)

$$\left[1 + I_1 T \left\{ \frac{\varphi_1(t) - \varphi_1(t-T)}{T} \right\} \right](1-A) = 1 + I_2 T \left\{ \frac{\varphi_2(t) - \varphi_2(t-T)}{T} \right\} \quad (257)$$

and making T tend to zero, we obtain

$$\left[1 + c_1 D_0 \frac{d\varphi_1(t)}{dt}\right](1-A) = 1 + c_2 D_0 \frac{d\varphi_2(t)}{dt} \quad (258)$$

or

$$D_0 = \frac{A}{(1-A)c_1 \frac{d\varphi_1(t)}{dt} - c_2 \frac{d\varphi_2(t)}{dt}}, \quad (259)$$

in which t is the time at which the local excitatory disturbance is maximal, and at which $x_2(t) = 1 - A$.

In equation (255) we have in the first place $\lim_{T \to 0} x_1(T) = 1$.

Furthermore

$$\lim_{T \to 0} e^{I_0 \int_0^t \left[1 + I_1 T \left\{ \frac{\varphi_1(u) - \varphi_1(u-T)}{T} \right\} \right] du} = e^{I_0 t + I_0 c_1 D_0 \int_0^t \frac{d\varphi_1(u)}{du} du} =$$

$$= e^{I_0 \{t + c_1 D_0 \varphi_1(t)\}} \quad (260)$$

In the same way the other integral of (255) will become for $T \to 0$

$$I_0 \int_0^t \left\{ 1 + c_2 D_0 \frac{d\varphi_2(u)}{du} \right\} e^{\int_0^u I_0 \left\{ 1 + c_1 D_0 \frac{d\varphi_1(v)}{dv} \right\} dv} du =$$

$$I_0\int_0^t \left\{ 1 + c_2 D_0 \frac{d\varphi_2(u)}{du} \right\} e^{I_0\{u+c_1D_0\varphi_1(u)\}} du \tag{261}$$

Therefore finally we obtain

$$e^{I_0\{t+c_1D_0\varphi_1(t)\}}(1-A) = 1 + I_0\int_0^t \left\{ 1 + c_2 D_0 \frac{d\varphi_2(u)}{du} \right\} e^{I_0\{u+c_1D_0\varphi_1(u)\}} du \ldots \tag{262}$$

The two equations (259) and (262) produce together the Constant Quantity D_0 and the time at which the excitation originates. Since D_0 can, with the help of (259), be inserted directly into (262) an equation in t is consequently found. The solving of t from this equation is once again not feasible. It is even impossible to determine t numerically for given n_1, n_2, τ_1, τ_2, and A.

In one single case we may advance a little viz., in case the assimilation of X should develop earlier than the dissimilation and on the assumption that with very short current-pulses the change in the rate of dissimilation, is negligible.

In this case (259) (in which $-A$ is substituted for A) will become:

$$D_0 = \frac{A}{c_2 \frac{d\varphi_2(t)}{dt}} = \frac{Ae^{n_2t}\Gamma(n_2\tau_2)}{c_2n_2(n_2t)^{n_2\tau_2-1}} \tag{263}$$

Equation (262) will become

$$e^{I_0t}(1 + A) = 1 + I_0\int_0^t \left[1 + c_2D_0 \frac{d\varphi_2(u)}{du} \right] e^{I_0u} du$$

$$= e^{I_0t} + \frac{c_2I_0D_0}{\Gamma(n_2\tau_2)} \int_0^t e^{I_0u} n_2 e^{-n_2u} (n_2u)^{n_2\tau_2-1} du$$

$$= e^{I_0t} + c_2I_0D_0 \times \frac{n_2^{n_2\tau_2}}{(n_2-I_0)^{n_2\tau_2}} \times \Gamma_{(n_2-I_0)t}(n_2\tau_2) \tag{264}$$

Further manipulation gives

$$\frac{c_2I_0D_0e^{-I_0t}\,\varphi_{(n_2-I_0)t}(n_2\tau_2)}{\left(1-\frac{I_0}{n_2}\right)^{n_2\tau_2}} = A \tag{265}$$

Inserting D_0, we obtain

$$\frac{I_0 e^{-I_0 t}\,\Gamma_{(n_2-I_0)t}(n_2\tau_2)}{\left(1-\frac{I_0}{n_2}\right)^{n_2\tau_2}\Gamma(n_2\tau_2)} \times \frac{t\Gamma(n_2\tau_2)e^{n_2 t}}{(n_2 t)^{n_2\tau_2}} = 1$$

or

$$\frac{I_0 e^{(n_2-I_0)t}\,\Gamma_{(n_2-I_0)t}(n_2\tau_2)}{t^{n_2\tau_2-1}(n_2-I_0)^{n_2\tau_2}} = 1 \tag{266}$$

From this equation t is to be solved. It should be noticed, that A is absent from this equation.

Putting $(n_2 - I_0)t = p$ and $n_2\tau_2 = q$, we can simplify further to

$$\frac{e^p\Gamma_p(q)}{p^{q-1}} = \frac{n_2-I_0}{I_0} \tag{267}$$

whence p should be deduced.

It is now possible to elaborate certain numerical cases in order to obtain a comparison with the provisional solution of Chapter II, in which the excitation originated at the time τ_2.

As we might have expected, values $t > \tau_2$ are found.

5. Exponentially rising currents

If the constant current produces many mathematical difficulties, the more so variable currents.

I shall therefore elaborate one single case viz., that of the exponentially rising currents, because in this case the magnitude λ, HILL's time-factor of accommodation, appears. In the former treatments λ was always less than the H.N.Z., which was contrary to the experimental results. I shall now demonstrate that, using the generalized equations, it may be much larger than the H.N.Z.

In order to simplify the formulae I shall only treat the case that $c_1 = c_2$ (electrotonic complications will not occur).

Now

$$ci(t) = I(1 - e^{-\frac{t}{\alpha}}) \tag{268}$$

According to (240) therefore

$$I(t) = I\int_0^t (1 - e^{-\frac{t-\theta}{a}})\alpha(\theta)d\theta$$

$$= \frac{In_1^{n_1\tau_1}}{\Gamma(n_1\tau_1)}\int_0^t (1 - e^{-\frac{t-\theta}{a}})e^{-n_1\theta}\theta^{n_1\tau_1-1}d\theta \tag{269}$$

$$\text{and } L(t) = \frac{In_2^{n_2\tau_2}}{\Gamma(n_2\tau_2)}\int_0^t (1 - e^{-\frac{t-\theta}{a}})e^{-n_2\theta}\theta^{n_2\tau_2-1}d\theta \tag{270}$$

Putting

$$K_1 = \frac{n_1^{n_1\tau_1}}{\Gamma(n_1\tau_1)} \text{ and } K_2 = \frac{n_2^{n_2\tau_2}}{\Gamma(n_2\tau_2)}, \tag{271}$$

the equation for the Relative Concentration of X will be as follows

$$\frac{dx(t)}{dt} = -I_0\left\{1 + K_1 I\int_0^t (1 - e^{-\frac{t-\theta}{a}})e^{-n_1\theta}\theta^{n_1\tau_1-1}d\theta\right\}x(t) +$$

$$+ I_0\left\{1 + K_2 I\int_0^t (1 - e^{-\frac{t-\theta}{a}})e^{-n_2\theta}\theta^{n_2\tau_2-1}d\theta\right\} \tag{272}$$

Excitation for threshold-value occurs if $\frac{dx(t)}{dt} = o$ and just at this moment $x(t) = 1 - A$ (case of dissimilation occurring before assimilation). It follows therefore

$$\left\{1 + K_1\frac{I}{a}\int_0^t a(1 - e^{-\frac{t-\theta}{a}})e^{-n_1\theta}\theta^{n_1\tau_1-1}d\theta\right\}(1 - A)$$

$$= 1 + K_2\frac{I}{a}\int_0^t a(1 - e^{-\frac{t-\theta}{a}})e^{-n_2\theta}\theta^{n_2\tau_2-1}d\theta \tag{273}$$

We must find again $\lim_{a\to\infty} \frac{I}{a} = \mu$, at which $t = t_\infty$.

For large a we may replace $1 - e^{-\frac{t-\theta}{a}}$ by $\frac{t_\infty - \theta}{a}$.

We obtain therefore

$$\left\{ 1 + K_1\mu \int_0^{t_\infty} (t_\infty - \theta) e^{-n_1\theta} \theta^{n_1\tau_1 - 1} d\theta \right\} (1 - A)$$

$$= 1 + K_2\mu \int_0^{t_\infty} (t_\infty - \theta) e^{-n_2\theta} \theta^{n_2\tau_2 - 1} d\theta \qquad (274)$$

Integration with due allowance for the values of K_1 and K_2 produces

$$[1 + \mu \left\{ t_\infty \varphi_{n_1 t_\infty}(n_1\tau_1) - \tau_1 \varphi_{n_1 t_\infty}(n_1\tau_1 + 1) \right\}] (1 - A)$$

$$= 1 + \mu \left\{ t_\infty \varphi_{n_2 t_\infty}(n_2\tau_2) - \tau_2 \varphi_{n_2 t_\infty}(n_2\tau_2 + 1) \right\} \qquad (275)$$

whence

$$\mu = \frac{A}{(1-A) \left\{ t_\infty \varphi_{n_1 t_\infty}(n_1\tau_1) - \tau_1 \varphi_{n_1 t_\infty}(n_1\tau_1 + 1) \right\} - \left\{ t_\infty \varphi_{n_2 t_\infty}(n_2\tau_2) - \tau_2 \varphi_{u_2 t_\infty}(n_2\tau_2 + 1) \right\}} \qquad (276)$$

Writing $R = c\Delta$, from (252) we know ($c_1 = c_2 = c$)

$$R = \frac{A}{(1 - A)\varphi_{n_1 T_H}(n_1\tau_1) - \varphi_{n_2 T_H}(n_2\tau_2)} \qquad (277)$$

Therefore

$$\lambda = \frac{R}{\mu} = \frac{(1-A) \left\{ t_\infty \varphi_{n_1 t_\infty}(n_1\tau_1) - \tau_1 \varphi_{n_2 t_\infty}(n_1\tau_1 + 1) \right\} - \left\{ t_\infty \varphi_{n_2 t_\infty}(n_2 t_2) - \tau_2 \varphi_{n_2 t_\infty}(n_2\tau_2 + 1) \right\}}{(1-A)\varphi_{n_1 T_H}(n_1\tau_1) - \varphi_{n_2 T_H}(n_2\tau_2)} \qquad (278)$$

That this value of λ is generally larger than in the theory developed first, can be shown as follows:

If the assimilation develops much more slowly than the dissimilation, we may neglect the terms with the index n_2. If τ_1 is very small and n_1 very large, we may put $\varphi_{n_1 t_\infty}(n_1\tau_1) \sim 1$ and $\varphi_{n_1 T_H}(n_1\tau_1) \sim 1$ and neglect also the term with the factor τ_1.

Now (278) reduces to

$$\lambda \sim t_\infty \qquad (279)$$

In case the dissimilation develops much more slowly than the assimilation the same result is obtained.

It is evident from the already classical measurements by K. LUCAS (1907), GILDEMEISTER (1913) and LAPICQUE (1926), that the utilization-time with linearly and exponentially rising currents, near the minimal current-gradient, is in fact of the same order as the λ measured subsequently (for the frog's sciatic nerve of the order ten times the H.N.Z.).

6. Chweitzer's scheme

The following discrepancy between the original theory and the experiment was found in CHWEITZER's scheme. Using the generalized equations, we encounter again some serious mathematical difficulties but yet we can demonstrate the possibility of the new theory to explain the characteristic properties of CHWEITZER's scheme.

I shall restrict myself to the phenomena with catelectrotonus and only treat the case that the assimilation develops quicker than the dissimilation. In the opposite case the same result is obtained.

Let i be the current-strength of the conditioning current and Δ_i the appropriate Rheobase in catelectrotonus, then the equation of metabolism will be:

$$\frac{dx_1(t)}{dt} = -I_0 \left\{ 1 + c_1 i + c_1 \Delta_i \varphi_1(t) \right\} x_1(t) + I_0 \left\{ 1 + c_2 i + c_2 \Delta_i \varphi_2(t) \right\} \quad (280)$$

At the moment $T_{H,i}$, when the local excitatory disturbance is maximal, we have

$$\left.\frac{dx_1(t)}{dt}\right|_{t=T_{H,i}} = 0 \text{ and } x_1(T_{H,i}) = 1 + A, \text{ while } x_1(0) = \frac{1 + c_2 i}{1 + c_1 i} > 1 .$$

So $T_{H,i}$ is therefore the H.N.Z. concomitant of the conditioning current.

Condition $\left.\frac{dx_1(t)}{dt}\right|_{t=T_{H,i}} = 0$ now produces

$$\left\{ 1 + c_1 i + c_1 \Delta_i \varphi_1(T_{H,i}) \right\} (1 + A) = 1 + c_2 i + c_2 \Delta_i \varphi_2(T_{H,i}) \quad (281)$$

Hence

$$\Delta_i = \frac{(1 + c_1 i)(1 + A) - (1 + c_2 i)}{c_2 \varphi_2(T_{H,i}) - c_1(1 + A)\varphi_1(T_{H,i})} \tag{282}$$

Comparing this result with the extensively discussed case of Chapter II p. 82, we found that in the latter case (substituting $c_2\Delta_0 = A$ in (173))

$$\Delta_i = \frac{(1 + c_1 i)(1 + A) - (1 + c_2 i)}{c_2} \tag{283}$$

If $c_1(1 + A) > c_2$, Δ_i rose here linearly with i. In the new solution the numerator will, on the same condition, increase linearly too. But now the functions $\varphi_1(T_{H,i})$ and $\varphi_2(T_{H,i})$, which are likewise functions of i, appear in the denominator.

In order to determine Δ_i as a function of i, we have to eliminate $T_{H,i}$ from (282) and the other relation $x_1(T_{H,i}) = 1 + A$, which is again mathematically impossible.

The latter is not needed however to make us realize, that under certain circumstances Δ_i *will indeed, for increasing i, at first decrease from* $i = 0$ *in order to rise afterwards.*

For, if we consider the function (denominator of (282))

$$f(t) = c_2\varphi_2(t) - c_1(1 + A)\varphi_1(t) \tag{284}$$

in the interval $0 < t < \infty$, we find that the two functions $\varphi_1(t)$ and $\varphi_2(t)$ will increase in this interval, both from 0 to 1. In the proposed case we shall always have $\varphi_2(t) > \varphi_1(t)$, while furthermore $\varphi_2(t)$ rises much earlier and much quicker to 1.

The function $f(t)$ therefore has a maximum in this interval for $t = T_{H,max}$.

Now suppose, that $T_{H,o} > T_{H,max}$ and that for increasing i, $T_{H,i}$ also increases. In that case the numerator of Δ_i (282) will indeed increase with i, but the denominator will likewise increase and go through its maximum, so that there is a fair chance that Δ_i will at first diminish in order to rise to ever-increasing values afterwards. The latter follows from the fact that

$$\Delta_i > \frac{(1 + c_1 i)(1 + A) - (1 + c_2 i)}{c_2} \tag{285}$$

always.

The same possibility exists, if it should be that $T_{H,i} > T_{H,max}$ while

for increasing i, $T_{H,i}$ decreases, for in this case too, the denominator of Δ_i will go through its maximum for increasing i. In view of the difficulty in determining $T_{H,i}$ as a function of i, a further discussion of the conditions under which Δ_i will at first decrease must be omitted for the present. If it should ever be possible to discover these conditions, then we should be in a position to know a little more about the influence which certain ions ($K^{\cdot}$ of $Ca^{\cdot\cdot}$) have on the various magnitudes which play a part in the equation of metabolism. Meanwhile it must be granted, that the generalized equations provide a reasonable explanation of CHWEITZER's scheme.

Further, a more important conclusion may yet be drawn from the above discussion.

If we assume, that the initial fall of Δ_i with increasing i is the result of the fact that $T_{H,i}$ also increases, it follows that, even for $i = o$ and $t = T_H$, the function $\varphi_2(T_H)$ will not be near in value to 1, in other words, that the assimilation-coefficient also ascends much more gradually to the limit 1 than was at first supposed. The dissimilation-coefficient will of course do so even more gradually in the case treated now.

To be sure, an enhancement of T_H to $T_{H,i}$ must have the effect, that Δ_i at first decreases.

This solves a question which with the ion-theories has always aroused criticism. For UMRATH (1925) has pointed out, that the movement of the ions in their environment under the experimental circumstances is much slower than the existing ion-theories (NERNST, HILL, FABRE etc.) demand. Also GONDET (1932) was inclined to decide from his experiments, that although very short current-pulses can excite, the ions experience only submolecular displacements.

Apart from the question whether the latter statement is quite correct, it appears from our theory that excitation can occur long before the ion-concentrations have reached their limit-values.

In the case where $T_{H,i}$ should decrease with increasing i, the inference might not seem to be so conclusive, but we may then conclude, that for a very weak conditioning current i, $\varphi_2(T_{H,i}) \ll 1$, so that it would indeed be very unlikely that $\varphi_2(T_H)$ would have a value very near 1. It stands to reason that the reflections on CHWEITZER's scheme lead to the same conclusions, where the dissimilation of X develops more quickly than the assimilation.

V

SUMMARY AND CONCLUSIONS

After the gradual development of the theory we may now briefly repeat and summarize the purpose and results in order to see clearly the essential conclusions.

If one studies the many theories which have been framed in the course of time about the local excitation of nerve, then it attracts our attention that they all start from purely physical models. Now it is obvious that the nerve consists of very many chemical substances and that certain chemical reactions may take place. Likewise, the nerve has very definite physical properties like resistances and capacitances. But a nerve is not a test-tube or a system of resistances and capacitances. It is more! It is a living object and this means that there is always something going on, even when we are not experimenting at all. And when we are sending a current through part of the nerve, we intervene in this dynamical system. The events mentioned, connected with Life, will be differently influenced at the various points of the nerve, and an excitatory disturbance may originate along the whole nerve. If the current-pulse is so strong that the resulting disturbance exceeds a certain value at some point or other, or, if necessary within a certain distance of this point, then the whole system will collapse and an excitation-wave will be propagated along the nerve. This is the main principle of this theory.

It is another question, what distinguishes living matter and so also the nerve from the dead physical or chemical model. The only thing we know definitely is that in each living object there is a continuous building up and breaking down of all kinds of essential substances (called biogenic). From the milieu, new matter is continuously supplied and other substances are broken down, during which various energy-transformations play a part. In other words, it is metabolism which is characteristic of life. Mostly, when speaking about metabolism, one thinks of certain chemical reactions and its value is determined according to this energy. However, I pointed out, that when speaking about metabolism we may also think of a continuous activation and inactivation of enzymes and when an ion or even an electron is attached to a protein-

molecule this event may be considered an assimilation and the severing of a similar connection a dissimilation. So in the case of the nerve, the attachment of an ion or an electron to the membrane and the releasing of it may be called matters of assimilation and dissimilation, if we only remember that these events occur continuously and also when we are not experimenting at all. Hence the excitatory disturbance caused by an electric current consists of an alteration of the dynamical equilibrium between assimilation and dissimilation of "a certain biogenic subtance X", which will be responsible for the occurrence of an excitation-wave, if its concentration at one point or another reaches a determined value, smaller or larger than the normal one. Regarding the nature of this substance X, nothing is assumed and after what has just been said about metabolism one may think of it what one likes. But now I assume that in the neighbourhood of the cathode the dissimilation-velocity as well as the assimilation-velocity will gradually change to new values, if a constant current of sufficiently long duration is sent through part of the nerve. These new values, which will be functions of the intensity of the current as well as of the concentration of X itself and of the concentration of new-matter present, will not be reached immediately after the closing of the current. According to displacements of ions in a colloidal milieu, collisions with more or less energy and other events which will only occur with a certain probability, will develop only gradually. For dissimilation and assimilation they will do that in their own way.

If the current is cut off, both processes return, again each in their own way, to normal circumstances.

In the neighbourhood of the anode similar things occur; except that the changes in the rate of dissimilation and assimilation have the opposite direction. And in all other points of the nerve we shall find the same kind of changes, but in each point these changes will have their own development.

In order to put the above reflections to the test experimentally, it was necessary to introduce mathematics and so we came to the following hypothetical equation of metabolism, which, of course, could only be a first approximation.

Let $\xi(t)$ be the concentration of the biogenic substance X and $\varrho(t)$ the concentration of the matter from which X is built up, then, for not too great intensities, we may write for the cathode

$$\frac{d\xi(t)}{dt} = -I_0 \left\{ 1 + I(t) \right\} \xi(t) + L_0 \left\{ 1 + L(t) \right\} \varrho(t)$$

and for the anode, approximately

$$\frac{d\xi(t)}{dt} = -\frac{I_0}{1 + I'(t)} \xi(t) + \frac{L_0}{1 + L'(t)} \varrho(t)$$

in which

$$I(t) = c_1 \int_0^t i(t-\theta)\alpha_1(\theta)d\theta \text{ and } L(t) = c_2 \int_0^t i(t-\theta)\alpha_2(\theta)\, d\theta$$

$$I'(t) = c_3 \int_0^t i(t-\theta)\alpha_3(\theta)d\theta \text{ and } L'(t) = c_4 \int_0^t i(t-\theta)\alpha_4(\theta)d\theta$$

In these formulae $i(t)$ means the current-strength at the time t. The coefficients of $\xi(t)$ and $\varrho(t)$ are called respectively the dissimilation- and assimilation-coefficient.

The fact that both coefficients at every point of the nerve are developing in their own way, could be characterized by using POISSON's functions for $\alpha(\theta)$.

So we see that for a constant current of sufficiently long duration, at the cathode the dissimilation- and assimilation-coefficients gradually develop from I_0 to $I_0(1 + c_1 i)$ and from L_0 to $L_0(1 + c_2 i)$.

All that has been said so far must be considered essential to the theory and from the equations above, all phenomena of local excitation could be explained.

Although not essential in itself, it is however of some importance that this theory should not be considered as a piece of mathematical biophysics only, but also that several possibilities should be taken into consideration which may throw some more light upon the causes of the phenomena considered.

Hence the idea has been put forward that dissimilation- and assimilation-velocity may depend on the activating influence of different kinds of anions. One is especially reminded of the antagonism of $K^{\cdot}$ and $Ca^{\cdot\cdot}$ ions. By means of the potential-difference and the resulting current there will certainly be changes in the concentrations of the different ions, especially of the anions. We need not suppose that these displacements are so great as in NERNST's model or in the over-simplified model we ourselves started from. The dis-

placements may be very small and may occur only in the immediate environment of the membrane, where they give rise to polarisation- and depolarisation-phenomena respectively. One may further assume that the coefficients I_0 and L_0 are proportionate to the concentrations of the ions mentioned before the experiment starts, when everywhere along the nerve there is a steady state and the concentration of the biogenic substance X has everywhere the same value. Then the changes of these concentrations in the course of time will be approximately characterized by the functions $I(t)$ and $L(t)$.

For the explanation of the local excitation-phenomena it is not necessary to suppose anything about the different changes in the concentrations of the ions in all points of the nerve, but one can suffice with cathode and anode.

It will be clear, however, that the displacement of the ions in the different points of the nerve will keep up with the development of the physical electrotonus along the whole nerve, starting from the points where lines of force enter or leave viz. anode and cathode. In this respect, there is no divergence from all that has been found in the study of the passive phenomena.

However attractive it may be to include the antagonistic activity of $K^{\cdot}$ and $Ca^{\cdot\cdot}$ ions in the theory, it may be repeated once more, that the supposed properties of these ions are not essentially necessary for the theory. The physiologist, who is accustomed to regard all excitation-phenomena purely electrically, will even more readily regard the assimilation as an attachment of a charge to the membrane and the dissimilation as the releasing of it, for in this case the concentration of the biogenic substance X will be proportional to the electrical density at this point. Then our theory joins all theories which, starting from the core-conductor model, are concerned with the explanation of the passive properties of the nerve and the way in which excitation propagates according to time and space (RUSHTON). These theories do not contradict. On the contrary, they supplement each other. However, let us return to the essentials of the theory and its results.

It is assumed that for fresh and carefully prepared preparations, the concentration of the buildings-blocks $\varrho(t)$ is constant (ϱ_0) before the experiments and remains so during and after these experiments.

Before the experiment, the concentration of the biogenic sub-

stance X will be everywhere the same and constant (ξ_0). During and after the experiment, the current causes changes everywhere in this concentration. Now, it is assumed that excitation will occur in one point or other if the concentration of X reaches a certain critical value. It does not follow from the application of the theory to the experiments, that this critical concentration will be larger or smaller than the original one. Both possibilities exist, depending on the fact whether the change in the assimilation develops sooner than the change in the dissimilation or opposite.

With the above-mentioned hypothesis about a critical concentration the theory is complete and now we can see what it can do. It turns out that all the phenomena of local excitation can be explained: the phenomena at make and break, the strength-duration curves for all kinds of currents and, as far as could be calculated, their numerical relations, the constant-quantity-relation, the accommodation-phenomena with the minimal gradient, the état d'excitation, the phenomena of Physiological Electrotonus and last but not least, the peculiarities of CHWEITZER's scheme, for the latter scheme has properties which cannot be explained by any other theory. It concerns the peculiarity that the Rheobase Δ_i which is superimposed in the same direction on the "conditioning current" i, after the nerve has been accommodated, will provisionally decrease with increasing i. After having reached a flat minimum it furthermore increases to ever larger values with increasing i. As far as I know this theory is the only one which accounts for this phenomenon (page 121).

There is more: From the fact that the critical amplitude is reached after a "critical time", which is greater than the "Nutzzeit", it follows that there is time left to prevent excitation by a sufficiently strong opposite current-pulse*.

No theory accounts for this phenomenon except RUSHTON's, which, however, starts exactly where this theory stops. This once again leads us to a comparison with the purely electrical theory. It is true, in the theory developed here, the origin of action-currents and potentials has been left out of consideration, just as the causes of propagation of the excitation, but every change in the metabolism in a certain point—say the cathode—must certainly be accompanied by electrical phenomena in the environment of that point, which, in

* This will only be true according to the generalized equations and not according to the simplified ones we started from.

their turn, will cause changes in the metabolism of that environment etc.

So the complementary principle lies in the fact that the "resting potential" is not something statical, but only the expression of a steady state, which masks the restless building up and breaking down which is characteristic of Life.

The general equation of metabolism may be approximately right for every point of the nerve, but the various constants, appearing in the various functions must have different values. About the numerical values of these constants, even for a single point like the cathode nothing can be told. We are dealing only with the qualitative description of the numerous phenomena. Notwithstanding, it would be very interesting if we could express the numerical values of some of these constants. But several insurmountable mathematical difficulties appear to exist and we should be very pleased if professional mathematicians would study this equation thoroughly. Of how great importance it would be, for instance, if we could describe the general strength-duration curve as an explicit function, especially if this were possible in the extended case that the different threshold-currents are superimposed on a "conditioning current". Experiments as carried out by BOUMAN, in which these strength-duration curves were determined under various conditions of the milieu, would then give rise to valuable conclusions about the part played by different ions ($K^{\cdot}$ and $Ca^{\cdot\cdot}$).

And if one should succeed in expressing the "critical time" explicitly, a further testing of the experiments of RUSHTON and KATZ about the excitability after a single very short conditioning shock would be possible.

Finally, I may answer in advance some critical remarks which certainly will be expressed. People will say: "You have made your equation of metabolism so flexible, especially by introducing the Poisson-functions, that it may be possible to explain everything you like".

I may answer:

1. All results obtained are independent of the constants occurring in the formula, including those which determine the course of the Poisson functions.

2. Although it is of no importance for the qualitative results in which way the Poisson functions rise, the sigmoidal shape of their courses is necessary. For, if we replace them, for instance, by exponentially rising functions, these qualitative results would not be obtained. There would be no rheobase, nor could the equation account for the accommodation phenomena etc.
3. In the variability of the various constants the biological variability is expressed. In biology, universal constants cannot be expected and neither will it be possible to find very simple expressions containing only one or two parameters, to account for the multitude of properties of the simplest biological object.

PART III

BIOLOGICAL REACTIONS CAUSED BY X- AND γ-RAYS

I

INTRODUCTION

1. General aspects of the problems

The phenomena discussed in the preceding chapters referred to one special object only, the nerve, and to only one special effect, the generation of a muscle-contraction. Yet the nerve is such a complicated mechanism, that it is practically impossible to obtain a more or less complete physical model-representation.

The experiments considering the reactions evoked by X-rays, however, refer to all possible sorts of objects and phenomena. The objects vary from various types of isolated cells to the most complicated object, man. The effects examined are of all kinds.

In part, the experiments aim at gaining an insight into the dose and the way it is being applied, in connection with the coming into being of a certain irreversible effect such as the killing of a living cell, the obtaining of mutations by irradiation of fertilized eggs, or to the temporary or permanent elimination of the activity of certain gland and other cells (epilation).

Other experiments trace the changes in the course of time in the functions of irradiated cells and organs on application of smaller or larger doses: changes in the growth-rate of certain fungus-cells, in the functions of the blood-forming organs, in the blood-pressure, in the amount of salts in the tissues, in the *pH* etc.

The greatest difficulty as regards a possible explanation is, apart from the extremely involved nature of living matter, that there are always more things irradiated than are aimed at. Even in the case of a single cell, the protoplasm together with the nucleus will in general be irradiated, although mention must be made of VINTEMBERGER's interesting experiments, which obviated these difficulties in a single case. With experiments on more highly organised individuals it is impossible to irradiate exclusively one organ. Also it has been proved, that the environment of the cell or of the organ, irradiated or not, often has a great influence on the behaviour of the object examined. Another difficulty is, that the primum movens is never observed, but always secondary phenomena, which are often the ultimate result of a long line of processes. If an irreversible

phenomenon is concerned, this does not matter. The death of a cell is intimately connected, for instance, with the effect of a primary injury. Reversible or conditionally-reversible effects may, in general, acquire an entirely different character in their temporary course from the primary changes; especially in cases where there are one or more primary effects at the same time.

It must be noted, that by reversible changes are meant changes in function or in anatomical composition which in due course return to their normal qualities. In this case the biological object will completely recover from the injury caused by the rays.

With conditionally reversible changes this recovery is only achieved to a certain extent.

Because it is always secondary effects that are observed, relaxation- or latency-times are constantly occurring. These, in general, are much longer than those encountered in the previous chapters and they vary from seconds to several weeks.

2. The primum movens

How far has our insight into the primum movens advanced? Unfortunately, we have to admit that practically nothing can be experimentally determined with any certainty about this matter. How intricate the problem is, appears from the fact that even with irradiation of lifeless substances we are up against at present unsolvable problems. Thus with irradiation of lifeless colloids very involved phenomena are found, like periodic and sometimes discontinuous changes. Even with experiments on the flocculating of albumins caused by X-rays, latency-times occur.

The nature of the primum movens furthermore depends entirely on the effect under examination. As regards cell-death there are numerous hypotheses which are in part too vague to be serviceable. Thus CASPARI supposes that poisonous substances, so-called necrohormones are formed, which cause cell-death; ELLINGER assumes the release of histamine-like substances, so-called H-substances, which are decomposed locally in the tissues.

NEMENOW was of opinion that Roentgen-energy always accelerated senescence of the living cell. He even thought that the energy absorbed would not play a part in this process, but that the electromagnetic field in itself could suffice (so-called Daseinswirkungen).

Of late FAILLA's theory has come to the fore and originates from the fact that X-rays generate ions and that these ions cause the destruction of certain albumins and so explains the swelling of irradiated cells to bursting by an increase of the osmotic pressure. This theory beautifully interprets the influence of the environment, where, likewise, ions are formed, which, however, by the circulation of the tissue-liquid are more easily removed.

It was, of course, understood long ago, that test-objects, which are to teach us more about the action of X-rays, should be as simple as

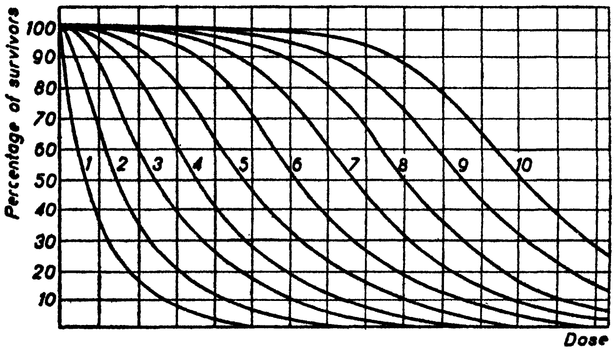


FIG. 26 – Typical survival curves for various objects. Each object has its own survival-curve.

possible. Since colonies of isolated, preferable homogeneous cells form a simpler object than a cell-complex, innumerable experiments have been made with such colonies, with some sharply-defined effect always being kept in view, e.g., the death of the cell, or the origin of a certain mutation.

If, by way of an example, a certain number of cells are killed by given doses of X-rays, the corresponding doses and the percentages of surviving cells can be graphically represented and it is remarkable, that with these statistical experiments the so-called survival-curves have their own particular character for each object and that they are occasionally exponential, but mostly sigmoidal (Fig. 26). In 1923 DESSAUER made an attempt to found thereon a theory of the biological action of X-rays. He relied on the quantum-structure of the X-rays and thought, that each absorbed Roentgen-quantum would increase the "temperature" of some specific albumin-molecule over a critical limit (Point-warmth).

He further assumed that in a given object, a certain effect would only be evoked, when a number of quanta, characteristic of this object and this effect, should have been absorbed.

DESSAUER's pupils BLAU and ALTENBURGER elaborated the theory mathematically and it appeared in fact, that with the statistical experiments the survival-curves must have the recorded shape.

Soon after, objections were made to the conception of point-warmth, but simultaneously general attention was drawn towards this problem and the result has been that the theory, which was since called "hit-theory", has been further expanded by many investigators (CROWTHER, MADAME CURIE, CONDON and TERRILL, GLOCKER, SOMMERMEYER, and many others).

One of the results was, that with a fair degree of probability it could be assumed, that the nucleus of each cell is the part most sensitive to rays. This is where the hits have to be scored in order to evoke cell-death.

The exact nature of a "hit" has not been ascertained by any means. Thus CROWTHER thinks that by a hit is to be understood the formation of an ion-pair in the nucleus of the cell. GLOCKER and SOMMERMEYER, on the other hand, maintain that a hit is determined by the transit of an electron through the nucleus or a certain part of it.

Very important are the conclusions regarding the occurrence of certain mutations. It has been fairly well established by TIMOFÉEFF-RESSOVSKI and ZIMMER, that the genes, the bearers of all hereditary and non-hereditary properties of the cell, are large albumin-molecules.

However important these results may be, the question of the primum movens generally remains unanswered, especially if more than one hit has to be scored. For we should like to know what this new ion-pair in the nucleus, or this transit electron, which in its turn perhaps originates new ions, does further.

3. The potency of recovery. Sievert's theory

How much more involved the working of the X-rays is, appears from the fact, that each biological object can recover from an injury —even if caused by X-rays—in greater or less degree and dependent,

of course, on the nature of the injury. Even in a single cell, this possibility of recovery has to be kept in view (RAJEWSKI and DANZER, 1936; LEA, 1938; REBOUL, 1939).

The importance of the capacity of restoration of living objects finds particular expression in X-ray therapy. The possibility of recovery is the reason that a large dose given once is more efficient than the same total amount split up into several portions, which are administered intermittently after certain intervals.

KINGERY (1920) has advanced certain opinions as regards the capacity of the skin to cure itself. He assumes, that by the irradiation toxic substances are generated, which are cleared away by the body. This toxin would disappear exponentially in the course of time. STENSTRÖM and MATTICK (1926), PFAHLER (1928), MARVIN (1934), HOFFMANN and REINHARD (1934), QUIMBY and MACCOMB (1937), and LEA (1938) by means of mathematical treatment have tried to obtain formulae, which are valuable for therapy. It appears, however, that they can only interpret the observed phenomena to a certain extent. Later authors among those mentioned above have dropped the idea of a toxin which is cleared away and prefer to adopt the conception of cumulative dose viz. a dose which, administered at a certain moment, would have the same effect as the several, actually administered previous doses.

SIEVERT (1941) used the property of recovery from irradiation in order to explain the occurrence of undulatory phenomena in all possible organs and functions, after a dose given once. So it is, for example, that the number of white blood-cells will at first decrease after a dose given once in order to rise afterwards above the normal amount and then gradually to diminish to normal.

SIEVERT assumed that, if a certain radio-sensitive matter X was exposed to X-rays with an intensity i, the number of elements of this matter X would change according to the equation

$$\frac{dx_i}{dt} = -Ix_i + R(x_0 - x_{t-\tau})$$

in which x_t constitutes the number of elements of X at the time t. I is proportional to the intensity i; R is a constant and a measure for the restoration-tendency.

Furthermore there is the latency-time τ, which means that the

restoration commences only some time after the irradiation has begun.

The above equation would only hold good during the irradiation. After the irradiation has ceased, X changes according to the equation

$$\frac{dx_i}{dt} = R(x_0 - x_{t-\tau})$$

As a matter of fact, periodical undulatory modifications of X originate according to the above equations. Depending on the magnitude of R and τ the amplitude of the oscillations may become smaller and smaller, so that in course of time a stationary condition reasserts itself. However, the amplitude may also become larger and larger. A metastable condition would then originate which would certainly lead to the destruction of the object.

The present author (1942) has tested SIEVERT's equations on the convergence and divergence respectively of their solutions and has found the following results:

1°. After an irradiation of finite duration, the chance of divergence, that is to say, of a metastable condition, will become greater, the greater R will become, i.e. the greater the restoration-tendency the greater the chance that the system will go wrong.

2°. With irradiation of an infinitely-long duration, for any value of R divergence will occur, if I is only sufficiently small. This is of course physically impossible.

These considerations have induced me to abandon SIEVERT's theory and to try to construct a new one (1942). In its primary outline this new theory was also very simple, but in my opinion it provided a much better interpretation of the experimentally ascertained phenomena than did SIEVERT's theory. In the attempts to correct the theory and to extend it, my attention was drawn to the analogy with the problems of electric stimulation of the nerve and to the astonishing fact, that it can also account for this very large group of phenomena. I consider this to be valuable support for the possible correctness of the fundamental ideas. Meanwhile, it goes without saying that with the expansion the theory has undergone, lesser modifications have cropped up which will come up for discussion in the course of this treatise.

II

METABOLISM UNDER THE INFLUENCE OF X-RAYS

1. Hypotheses to be used

a. In order to be able to tell something about the local action of X-rays on metabolism in the sense I attached to it in the general introduction, we have to consider:

Of whatever kind the different processes resulting from the irradiation may be, the primary cause is the formation of ions by the X-rays. If it is the metabolism of a certain biogenic substance X which is influenced by the X-rays, the ions formed will, either directly or indirectly, be the cause of a possible change of the dissimilation- as well as the assimilation-rate.

As, in the field of biological reactions caused by X-rays, we are dealing with all kinds of biological objects, we must consider the following complications: The rate of dissimilation of the *considered biogenic substance* X may always depend on the *number* of elements of X. The rate of assimilation, however, may also depend on the number of elements of X or it may not do so.

The former will be the case, if we consider an organ or a tumour, whose growth is caused by the dividing of the cells themselves. The latter will hold, if the radiosensitive substance is built up by another kind of matter and this will be mainly the case, if we are dealing with very "low" biogenic substances. We shall provisionally only discuss this second case, where we can use many of the formulae of the preceding part dealing with the excitation of nerve.

Now I particularly assume:

HYPOTHESIS I

If a certain biogenic substance is radio-sensitive, certain ions formed by the X-rays will, either directly or indirectly, be the cause of an enhancement of the dissimilation- and assimilation-coefficient.

If we irradiate with a constant intensity, then the number of ions will at first increase. However, the more ions accrue, the more ions

will neutralize each other. I assume, that in the long run a steady state will be reached, in other words:

Hypothesis II

With constant intensity of irradiation the concentrations of these ions will tend towards certain limiting concentrations, which, for a first approximation, may be proportional to the intensity itself.

In order to define the relation between these limiting concentrations and the dissimilation- and assimilation-coefficients respectively, now follows:

Hypothesis III

With an irradiation of infinitely long duration, the ultimate values of the dissimilation- and assimilation-coefficients will become proportional to the limiting concentrations of the various ions.

In other words: Ultimately, the dissimilation-coefficient in the resting-state I_0 will be enhanced to $I_0 + c_1 i$ and the assimilation-coefficient L_0 will also be changed to $L_0 + c_2 i$, if i is the intensity of the irradiation.

As in case of the electric stimulation of the nerve, one cannot expect, that instantly at the beginning of the irradiation both coefficients would jump to their ultimate values. They will only gradually develop as a result of different causes.

Firstly, the ion-concentrations themselves will need some time to reach their new values. But by then a notable time θ may elapse before an element of the considered biogenic substance X will be attacked and especially before a *new element of X* will be built up.

I again assume:

Hypothesis IVa

The ions formed by the X-rays will carry on their influence upon the dissimilation- and assimilation-coefficients respectively after a relaxation-time different for each ion.

HYPOTHESIS IVb

Any relaxation-times are possible, but there will be mean-values τ_1 and τ_2 for the dissimilating and assimilating ions respectively. The probabilities of a relaxation-time $\theta = 0$, and $\theta = \infty$ are assumed to be both zero.

Now the development of both coefficients may again be described approximately by POISSON's functions $\varphi_1(t)$ and $\varphi_2(t)$ and we obtain an equation of metabolism

$$\frac{d\xi(t)}{dt} = -\left\{ I_0 + c_1 i\varphi_1(t) \right\} \xi(t) + \left\{ L_0 + c_2 i\varphi_2(t) \right\} \varrho(t) \qquad (286)$$

in which $\xi(t)$ is the concentration of the biogenic matter X and $\varrho(t)$ the concentration of the building-blocks, present at time t, from which X is built up.

If the situation is such that during irradiation, $\varrho(t)$ does not change and if one starts from a steady state, the equation (286) can be substituted by

$$\frac{d\xi(t)}{dt} = -I_0 \left\{ 1 + \frac{c_1}{I_0} i\varphi_1(t) \right\} \xi(t) + L_0 \left\{ 1 + \frac{c_2}{I_0} i\varphi_2(t) \right\} \varrho_0 \qquad (287)$$

Putting again $\frac{\xi(t)}{\xi_0} = x(t)$ and $\frac{c_1}{I_0} = k_1$, $\frac{c_2}{L_0} = k_2$, then it follows from $I_0\xi_0 = L_0\varrho_0$ (11)

$$\frac{dx(t)}{dt} = -I_0 \left\{ 1 + k_1 i\varphi_1(t) \right\} x(t) + I_0 \left\{ 1 + k_2 i\varphi_2(t) \right\} \quad ..\, 0 < t < T \qquad (288)$$

in which T is the irradiation-time.

If the irradiation is stopped, the extra amount of ions produced by the X-rays will gradually disappear and analogous to the electric excitation of the nerve

$$\frac{dx(t)}{dt} = -I_0 [1 + k_1 i \left\{ \varphi_1(t-T) - \varphi_1(t) \right\}] x(t) +$$

$$+ I_0 [1 + k_2 i \left\{ \varphi_2(t-T) - \varphi_2(t) \right\}] \quad ....\, t > T \qquad (289)$$

approximately holds.

For irreversible changes I further add

HYPOTHESIS V

Irreversible changes may originate, if the value of the concentration of the biogenic matter X reaches a certain critical amplitude.

2. The limited applicability of the general equations

So the problem of the local biological reactions, caused by X-rays is reduced to the same equations as were found with the phenomena of electric excitation of nerve at the cathode.

Still there are some differences.

1°. In case of the electric stimulation of nerve there was only a displacement of the cations, in other words a polarization. So it was a question of already existing ions. That is why the increase of the concentration of these ions at the cathode was assumed to be proportional to the resting-concentrations I_0 and L_0.

As for the X-rays, without more ado ions, which will not need to be cations, are being formed and the increase of the ion-concentrations will be independent of I_0 and L_0.

2°. Since polarization is absent the equations regarding the anode are abandoned.

In a certain sense matters are therefore less complicated and we may use the mathematical results of the phenomena of electric excitation at the cathode only, writing $\frac{c_1}{I_0}$ for c_1 and $\frac{c_2}{L_0}$ for c_2 in the various formulae.

On the other hand, it is not a question anymore of one definite object and one definite effect, but of all possible reversible and irreversible phenomena and especially of more complicated ones.

In the first place, we have the question of the reserves. For the nerve we were in a position to assume, that with careful preparation they might be considered constant during the experiment.

With irradiation it will often happen, that together with the matter X which we intend to influence, the reserves also show alterations in response to the X-rays. So it is, that the observed effect may become entirely beyond control and complicated.

For the reversible and conditionally reversible changes there is furthermore another difficulty, as mentioned before. As regards the

perfectly reversible changes we are inclined to think, that in this case the equations (288, 289) can be applied without more ado, because the reversibility indicates that we can assume $\varrho(t)$ constant ϱ_0.

Now the primary effect will, in general, never be observed, but what can be recorded will always be a secondary effect. Also $\varrho(t)$ may undergo reversible changes, so that these secondary effects will apparently become much more complicated.

An example in point is the erythema of the skin caused by the irradiation, in which two, and on careful observation as many as three waves may occur (MIESCHER, 1924). This proves that different effects may be simultaneously active.

Even if by the irradiation only one definite substance is reversibly changed, so that $\varrho(t) = \varrho_0$, it may be possible, that the observed effect does not quite fit in with the primary equations of X, for we know that in many cases from a certain biogenic matter X develops another matter Y, and so on.

X may then be looked upon as the reserve of Y. It is now possible that the dissimilation- and assimilation-coefficients of Y do not change directly in response to the irradiation, but it is now the change of $\varrho_y(t)$, in this particular case $\xi(t)$, which, if necessary after a certain latency-time, generates the changes in Y.

For the conditionally reversible effects matters will become even more complicated.

From the preceding it follows that it will, in general, be very difficult indeed to apply the general equations to reversible or conditionally reversible changes. Although this will certainly be so, yet there are a number of reversible phenomena which can be explained excellently by the equations, because there seems to be chiefly one radiosensitive substance.

Before proceeding to a discussion hereof it should be noted, that it is not a question here of calculating the magnitudes present in the equations, but of testing the qualitative course, so that we are in a position to substitute for equations (288) and (289) the simpler one

$$\frac{d\xi(t)}{dt} = - I(t-\tau_1)\xi(t) + L(t-\tau_2)\varrho(t) \qquad (290)$$

which was at first also used for the electrical stimulation of nerve. Qualitatively this equation describes the phenomena equally well.

The problem of the nerve presented the question whether $\tau_1 > \tau_2$ or $\tau_1 < \tau_2$. It stands to reason, that this question obtains here as well. Nevertheless, henceforth I shall assume $\tau_2 > \tau_1$ i.e. I take it, that the X-rays cause destruction within a rather short time and that reconstruction follows only gradually.

Introducing the relative concentration $x(t) = \frac{\xi(t)}{\xi_0}$ again, and assuming that $\varrho(t)$ is constant, we may use once more the equation

$$\frac{dx(t)}{dt} = -I_0 \left\{ 1 + \frac{c_1}{I_0} i(t-\tau_1) \right\} x(t) + I_0 \left\{ 1 + \frac{c_2}{L_0} i(t-\tau_2) \right\} \quad (291)$$

for phenomena to be discussed.

At this moment I may point out a fundamental deviation from the theory which I had advanced in a simpler form previously. I then assumed, that the change in the assimilation-coefficient was a direct *result* of the change in the dissimilation-coefficient, in other words, that the decay of X called for a certain restoration. I proposed hypothetically, that the assimilation-coefficient with a certain retardation would always be proportional to the dissimilation-coefficient. In equation (291) this would resolve itself thus: that always $\frac{c_1}{I_0} = \frac{c_2}{L_0}$ and the equation would (if we put $\tau_1 = o$) reduce to

$$\frac{dx(t)}{dt} = -I(t)x(t) + I(t-\tau) \quad (292)$$

This hypothesis I have now completely abandoned. It is not only unnecessary and superfluous, but even unwanted.

I shall leave out of consideration the question whether there are any relations between a change of the dissimilation-coefficient and that of the assimilation-coefficient. Some ions may enhance the rate of dissimilation. Certain products of this dissimilation may stimulate the assimilation but I think it possible that some of the ions formed also have a stimulating influence upon the assimilation.

At any rate, the coefficients $k_1 = \frac{c_1}{I_0}$ and $k_2 = \frac{c_2}{L_0}$ are assumed to be generally independent of each other and may, even for specimens of the same kind, have different values.

III

THE EXPERIMENTS OF A. FORSSBERG

1. Results of the experiments

From the preceding reflections it follows, that, in general, it will be extremely difficult to find an object in which as regards a certain effect there will be chiefly one radio-sensitive substance whose reversible changes can be sufficiently accurately measured. We may search for such an effect in a higher individual or in a single cell.

A. FORSSBERG has in the course of years made a number of beautiful experiments on the fungus-cell *Phycomyces Blakesleeanus*. As long ago as 1925, BLAAUW and VAN HEYNINGEN demonstrated that this fungus reacts to extremely small dosages of X-rays with characteristic changes of growth-rate, properly called cell-stretching. The sporangium-bearer of this fungus grows normally with great and constant velocity. On X-iradiation, retardations and accelerations of the growth-rate occur. FORSSBERG has examined profoundly the course of these changes with time.

The provisional publication of his findings (1939) was already a starting-point for the first outline of the present theory.

Meanwhile, FORSSBERG has published an extensive report (1943) of his experiments and the new experiments described in it constitute another support of the hypotheses, at least in so far as they have been put forward in the present more extensive theory.

A first group of experiments relates to the irradiation of the fungus-cell for a short time with different intensities. It appears that

1°. The fungus-cell is extremely sensitive and reacts perceptibly to a dose of 0.0005 r.

Yet there are individual differences in the sensitiveness, which show themselves in a somewhat different course of the changes in the growth-rate.

2°. The changes in the growth-rate are reversible up to a dose of about 1000 r. For larger doses there are irreversible changes.

3°. The changes in the growth-rate begin to occur only after a latency-time of about 40 sec at 20° C. This time appeared constant for an intensity-interval of 1 to 2000.

For the rest the latency-time appeared to be dependent on temperature, while likewise it was found, that the latency-time is shorter in proportion as the normal individual growth-rate of the cell is greater.

4°. The course of the changes in the growth-rate is as follows (Fig. 27): After the latency-time there is always first a phase during which the growth-rate diminishes more and more and then increases considerably after a minimum has been reached. For many cells the

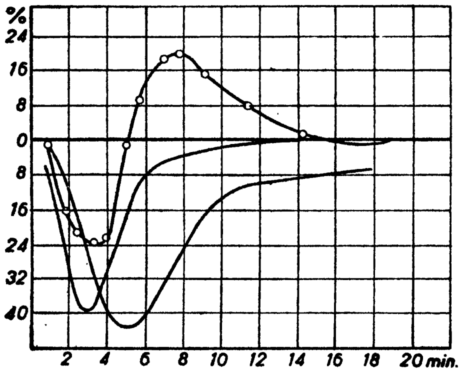


FIG. 27 – Experimental curves, showing the changes in the growth-rate, after a single irradiation, with different types of sporangium-carrieres of *Phycomyces Blakesleeanus*. – Ordinate: Change of growth-rate, expressed in percentage of the normal one. – Abscissa: Time in minutes. – Dose 2 r. Intensity 15 r/min. Irradiation time 8 sec. – A. FORSSBERG, *Acta Radiologica*, Suppl. XLIX.

normal growth-rate is exceeded and a phase originates in which the growth-rate increases. After having reached a maximum, the growth-rate gradually returns to the original value.

There are also cells, however, with which the phase of increased growth-rate fails to appear and the latter, after having reached the minimum, rises rapidly at first and then slowly to the normal value. So, in this case the course is monophasic.

In some cases, when the course is mainly diphasic, the first period is followed by a second very weak period. The latter only manifests itself clearly, when a first fairly weak retardation-phase is followed by a comparatively strong stimulation-phase.

5°. With experiments on one and the same cell both the amplitude

of the minimum and that of the maximum growth-rate appear to increase with increasing intensity. Both magnitudes, however, tend to limiting values. On application of doses above 1 r there are no obvious modifications of the effect.

6°. If with constant intensity the irradiation-time is continuously prolonged, the moment at which the growth-rate becomes minimal moves more and more to a certain limiting value.

The amplitude also increases continuously with this minimum and it likewise tends to a limit.

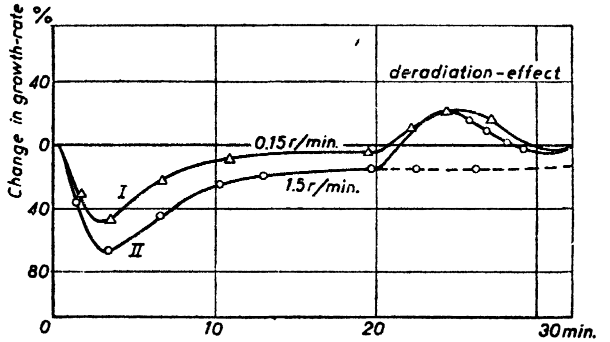


FIG. 28 – Two experimental curves by A. FORSSBERG for long irradiation time (20 min.) and deradiation effect. – I, 0.15 r/min. II, 1.5 r/min. – The dotted line shows the stabilization, if the irradiation is proceeded with after 20 min. – A. FORSSBERG, *Acta Radiologica*, Suppl. XLIX.

7°. If the irradiation is prolonged considerably (20 min), a monophasic course originates. After the growth-rate has decreased to a certain minimum, a new rise asserts itself and the growth-rate stabilizes itself at a new, generally lower level. For increasing intensity this level will be lower.

If the irradiation is stopped, a rise over the normal value up to a maximum occurs, after which a decline to the original normal value asserts itself (Fig. 28). This effect had already been observed by BLAAUW and VAN HEYNINGEN, who called it the "deradiation effect".

Apart from the above-mentioned experiments, FORSSBERG has carried out another series which concern the causes of the effect and the localization in the cell. He has discovered, inter alia, that:

1°. The primary reaction probably takes place in the wall of the

cell and thence propagates to a certain area, the growth-area which is situated just under the sporangium-capsule.

2°. The propagation-velocity can be determined and appears to be about 1.7 mm/sec, independent of the temperature.

3°. In the growth-area it appears that a coupling to certain receptors occurs, which leads to the visible phenomenon of growth.

4°. Whether the growth-area is also irradiated or not has no influence on the biological effect.

5°. The normal growth-rate depends on the temperature. Also the latency-time, which with constant temperature is independent of the intensity of the X-rays, appears to have a corresponding temperature-dependence.

6°. It is probable, that we have to do with a series of monomolecular reactions.

7°. The quantitative result of the reaction is independent of the size of the irradiated cell-volume, but depends on the concentration of the ions.

2. The second series of observations and the theory

From the above-mentioned series of observations about the causes of the various effects and the localization in the cell it follows that we have to conceive things as follows:

In the cell-wall there is a radio-sensitive biogenic substance X the reaction of which is determined by the equation (in simplified form)

$$\frac{d\xi(t)}{dt} = -I_0\left\{1 + k_1 i(t-\tau_1)\right\}\xi(t) + L_0\left\{1 + k_2 i(t-\tau_2)\right\}\varrho(t) \qquad (293)$$

This substance X or at least something proportional to the concentration of X, is conducted to the growth-area where there is another biogenic matter Y.

For the building up of Y the reserve-material is among other things determined by the concentration of X. Before the experiment, provided Y, like X, is considered to be in a (quasi-) steady state:

$$\frac{d\eta(t)}{dt} = -M_0\eta(t) + N_0\xi_0 \qquad (294)$$

holds for Y.

It now appears from the experiments, that the substances of the growth-area are not radio-sensitive.

If, therefore, X is modified by the irradiation, the equation for Y will become, in simplified form,

$$\frac{d\eta(t)}{dt} = -M_0\eta(t) + N_0\xi(t-\tau_3) \tag{295}$$

in which τ_3 is the time needed to propagate X or some effect of X. In the same way, another substance may be imagined, coupled to Y and the series may go on. Ultimately the chain ends with a biogenic matter U, the dissimilation-coefficient P_0 being negligible in comparison with the assimilation-coefficient Q_0, here better called the growth-coefficient. In this case, the latter matter U increases with a rapidity, which is proportional to the concentration of the immediately preceding reserve-matter. If the reserves which build up X are so great, that their concentration does not change during the experiment, notwithstanding the heavier charge, then always $\varrho(t) = \varrho_0$ and if, by careful preparation and by maintaining constant all possible external circumstances, the dissimilation- and assimilation-coefficients respectively become constant, the matter X and consequently all following biogenic substances Y, Z... will arrive at steady states. Except the latter U, because this matter—on account of the smallness of its dissimilation-coefficient P_0—only reaches the steady state at a moment very much later than the end of the experiment.

Let the thus-generated resting-concentrations be respectively ξ_0, η_0, ζ_0 etc., then (11)

$$\xi_0 = \frac{L_0\varrho_0}{I_0}$$

As before we obtain for X

$$\frac{dx(t)}{dt} = -I_0\{1 + k_1 i(t-\tau_1)\}\, x(t) + I_0\{1 + k_2 i(t-\tau_2)\} \tag{296}$$

in which $x(t) = \dfrac{\xi(t)}{\xi_0}$ represents the relative concentration of X.

From (294) follows that

$$\eta_0 = \frac{N_0\xi_0}{M_0}$$

Let $y(t) = \frac{\eta(t)}{\eta_0}$, then (295) will become

$$\frac{dy(t)}{dt} = -M_0 y(t) + M_0 x(t-\tau_3) \tag{297}$$

etc.

If we add to these reflections, that the observation of the quantitative effect which is dependent on the ion-concentration, is in accordance with the theory, as well as the possibility of monomolecular chemical reactions, then the second group of observations is also in accordance with the theory.

I now intend to examine, in how far the theory accounts for the first group of observed effects.

3. Comparison of the theory with the observed properties of the reactions

If we want to examine the course of the Relative Concentration of the primary radio-sensitive matter X during and after an irradiation of longer or shorter duration, we may, without more ado, link up with the results obtained in the part on the electrical stimulation of nerve in the case $\tau_1 < \tau_2$. Instead of the term "Local Excitatory Disturbance" we might even use here the more general term "Local Metabolic Disturbance" of the matter X.

It will therefore have the following course:

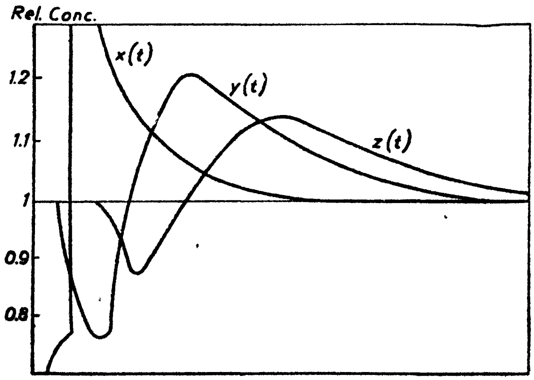


FIG. 29 – Changes of the Rel. Conc. of substances X, Y, and Z, coupled to each other, if only X is influenced by an irradiation applied in a negligible time ($c_1 = c_2$).

After the time τ_1 during which nothing seems to happen, the Relative Concentration of X decreases, during a time equal to the irradiation-time T, to the value $x(\tau_1 + T)$, and then rises afterwards till the moment $t = \tau_2$. Subsequently an increase above the normal value 1 asserts itself. From the time $t = \tau_2 + T$, the Relative Concentration of X decreases again to the original value 1. Thus the well-known diphasic curve originates.

The amplitude of the stimulating phase S $= x(\tau_2 + T)$ will depend on the magnitude of the multiplying constants k_1 and k_2. The smaller k_2 is with respect to k_1, the smaller S will be. If $k_1 \gg k_2$ the

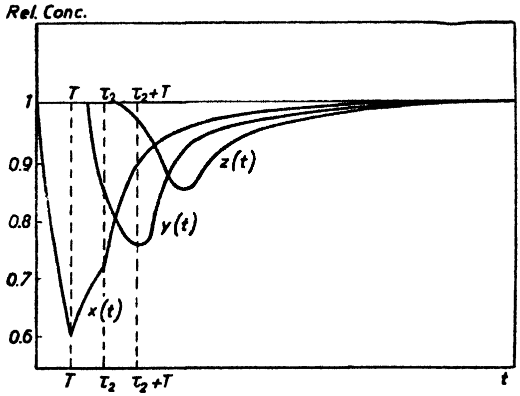


FIG. 30 – Changes of the Rel. Conc. of substances X, Y, and Z, coupled to each other, if only X is influenced by an irradiation applied in a short time ($c_2 \ll c_1$).

stimulating-phase may even fail to appear and the course will become monophasic.

Viewing the course of the Relative Concentration of Y, which in a certain sense reflects the course of X, we see that the elementary integrations—the rather tiresome formulae of which I shall spare the reader—produce a similar diphasic or monophasic course depending on k_1 and k_2. The reaction sets in after a latency-time $\tau_1 + \tau_3$.

There are however a few typical differences.

The minimum of X appears at the time $t = \tau_1 + T$; the minimum of Y, however, is not reached at the time $t = \tau_1 + \tau_3 + T$, as one might expect, but later. Also, the amplitudes of the relative concentration of Y are smaller than those of X, so that the curve has a shape

which wonderfully well resembles the one obtained from the experiment.

Advancing another step, and observing the reactions of a subsequent substance Z, we find that the latter possesses the same properties in a more enhanced degree.

In Fig. 29 one can see an example of the course of X, Y and Z, with negligible irradiation-time and in the case where k_1 and k_2 are about equal, in Fig. 30 in the case where k_2 is small against k_1.

In some cases the experimental curve, after having reached its maximum, does not decline asymptotically to the original value, but the first period is followed by another very weak one.

This slight discrepancy between theory and experiment can be easily explained, for FORSSBERG discovered that this phenomenon asserts itself when the stimulating-phase is very manifest. It has been assumed, that the reserves R of X do not change appreciably in the course of the experiment, so that we may always put $\varrho(t) = \varrho_0$. In the stimulating-phase, however, they are especially heavily charged and it is therefore probable, that the very weak second period owes its existence to the fact, that these reserves cannot stand the heavy charge without change. Another characteristic difference between the primary reaction of X and that of Y, Z etc. is the following, (with agreement of theory and experiment):

If we consider the minimum of $x(t)$, for which

$$x(\tau_1 + T) = \frac{1 + Ie^{-I_0(1+I)T}}{1 + I} \text{ for } T < \tau_2 - \tau_1 \text{ and } I = k_1 i,$$

as a function of the intensity i, then for increasing i this minimum-value will tend to zero, in other words, the minimum can reach any value between 1 and 0, if only we make i large enough.

The experiment (Fig. 31) yields the result, that for increasing i the minimum decreases indeed, but only to a certain limit: The calculation of the minimum of Y, however, produces exactly the same phenomenon, for we find that the minimum of Y is reached after a time t_1, which for increasing i tends to the limit t_∞:

$$t_\infty = \tau_1 + \tau_3 + T + \frac{1}{M_0 - I_0} lg \left[1 + \left(\frac{M_0}{I_0} - 1\right) e^{-M_0 T}\right]; \quad (298)$$

while for increasing i, y_{min} continuously decreases to the limit-value

$$y_{min,\,\infty} = 1 - \left[1 + \left(\frac{M_0}{I_0} - 1\right) e^{-M_0 T}\right]^{\frac{1}{1-\frac{M_0}{I_0}}} \tag{299}$$

In the case where t_∞ is greater than the time $\tau_2 - \tau_1 + \tau_3$ after which the enhanced assimilation-coefficient asserts itself, limiting-values are reached.

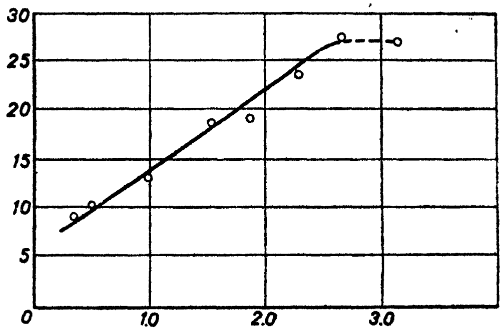


FIG. 31 – Changes of the amplitude of growth-rate inhibition by ever-increasing dose. – Ordinate: Utmost decrease of growth-rate, expressed in percentage of the normal growth-rate. – Abscissa: log (1000 dose in r). – A. FORSSBERG, *Acta Radiologica,* Suppl. XLIX.

Keeping the intensity constant, but increasing the irradiation-time up to and above the time $\tau_2 - \tau_1$, we find of course, that the stimulating-phase will be suppressed more and more. For very long irradiation-times the growth-rate will become stabilized at a level, which according to the theory is determined by the relative value

$$\frac{1 + k_2 i}{1 + k_1 i}$$

After the Relative Concentration of X, Y etc. have at first decreased to a certain minimum, they subsequently increase gradually to this value (Fig. 32. Fig. 23).

The course is therefore again in accordance with experiment. It appears at the same time, that for the fungus-cell examined $k_2 < k_1$, for the level is lowered in the accommodated condition and with increasing i it becomes ever lower.

Furthermore we have the deradiation-effect. This is also explained by the theory.

After adaptation has been achieved, for X, the equation

$$\left.\begin{aligned} \frac{dx_0(t)}{dt} &= -I_0(1 + k_1 i)x_0(t) + I_0(1 + k_2 i) \\ \text{holds with} \qquad x_0(t) &= \frac{1 + k_2 i}{1 + k_1 i} \end{aligned}\right\} \tag{300}$$

If the irradiation ceases, we first obtain (after τ_1 sec)

$$\frac{dx_1(t)}{dt} = -I_0 x_1(t) + I_0(1 + k_2 i) \tag{301}$$

and after τ_2 sec.

$$\frac{dx_2(t)}{dt} = -I_0 x_2(t) + I_0 \tag{302}$$

Hence it follows, as a matter of fact, that after the cessation of the irradiation an increase of the Relative Concentration of X ensues, which is followed by a decline towards the original value 1.

A similar sequence holds for Y and Z etc. (see Fig. 33, compare Fig. 28).

The fact that we often see the experimental curve dip just below the normal and then revert afterwards to the value 1, can again

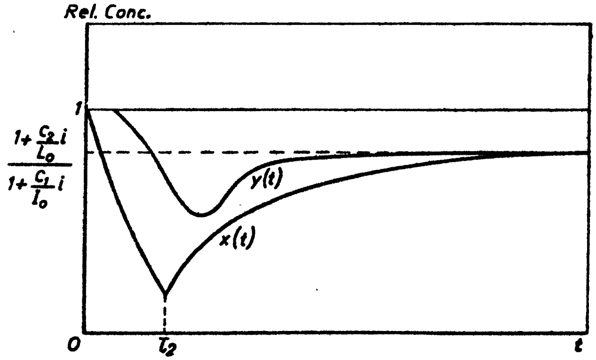


FIG. 32 – Changes of the Rel. Conc. of substances X and Y, coupled to each other, if only X is influenced by an irradiation of infinitely long duration ($c_2 < c_1$).

be explained in this way, that by the high charge the concentration of the reserves $\varrho(t)$ cannot be put exactly equal to ϱ_0, but that this heavier charge temporarily diminishes it a little.

Finally, a further word may be said about the fact that with doses of over 1000 r irreversible changes are observed. It seemed in every respect remarkable, that with heavy doses which approach this value, irreversible effects suddenly originated, while the biological effect had long before reached a definite limit-value.

FORSSBERG thought that next to the first reaction a new type came into being. In my opinion the phenomenon is founded on the fact that with the primary reaction a certain critical amplitude, at which part of the system breaks down is passed. I would draw attention to the point that, for increasing i, all amplitudes of $x(t)$ between 0 and 1 are possible. Since the amplitude with the secondary reactions tends to a limit for increasing i, this critical amplitude does not clearly show here.

Summarizing, we find that the theory gives a complete explanation of all phenomena observed by FORSSBERG, even although we use the approximate equations. The more general equations, in which the relaxation-times lose their original hypothetical significance, produce the same results.

Naturally there are questions which remain unanswered. We are not able to examine, whether we have to do with Y or with Z etc. and we do not know how long the chain has to be before the observed effect is generated.

It should be noted, that FORSSBERG has also found a few more particulars about the relationship between the amplitudes of the minima and maxima and about the areas above and below the axis of the two phases. Since I have not found these regularities in general very convincing as real properties of the reactions and since the calculations become extremely involved, I have left them out of consideration.

FORSSBERG has, in his book, compared the phenomena with SIEVERT's theory. Some experimental findings are described fairly well by SIEVERT's equations, others are not. There are furthermore the serious objections I mentioned before, which are a consequence of the easily occurring divergence of the solutions.

IV

OTHER REACTIONS

1. Reversible changes

That the theory is not only applicable to a single object like the particular cell first discussed, appears from the large number of oligo-phasic reversible reactions that occur in all possible forms and with all possible higher biological objects after a single Roentgen- and γ-irradiation. I want to draw special attention to a few of these.

KROETZ (1924), LACASSAGNE and LOISELEUR (1933) and REDING (1935) have determined the pH of blood and of irradiated tissues. It appears that in the first hours an acidosis occurs, which is followed after 24–28 hours by a prolonged alkalosis.

MELTZER and KÜHTZ (1938) irradiated rabbits with 825 r. They found a diphasic reaction in the amount of salts in skinpatches. After 7 hours a salt-increase manifested itself, which was maximal after 31 hours. Subsequently the amount of salts decreased below the norm, and then rose again to reach the normal value.

Many observations have been made about the mitotic activity of irradiated organs. Normally there is not a (quasi-) steady state in these cases. The mitotic activity shows a certain rhythm; discovered by LACASSAGNE and MONOU (1922) and confirmed by REGAUD (Testis-tissue), JÜNGLING (*Vicia faba equina*) and LANGENDORFF *et al.*

The existence of such rhythmical changes in the functions of certain organs does not detract from the theory. The calculations were made on the assumption that the experiments related to one radio-sensitive substance, the reserves out of which this substance was constructed being considered constant during the experiment. At the same time it was supposed that by keeping the external circumstances constant, both the assimilation- and dissimilation-coefficients were constant. In this case the biogenic matter, which possibly regulates a certain event, tends to a steady state. We do not know what is the cause of these periodic changes, but I notice that they occur about a mean value, which for the radio-sensitive substance may be taken equal to ξ_0 and that the rhythm, which is

probably of internal origin, seems to have no connection with the changes caused by the X-rays.

SPEAR and GLÜCKSMANN (1938) irradiated frog's larvae with γ rays for 70.5 minutes with a dose of 268 r. At different times after the irradiation they made preparations of the brain and eye and counted the number of cells which showed mitotic activity. They found:

1°. A period of reduced mitotic activity, 1–3 hours after the irradiation.

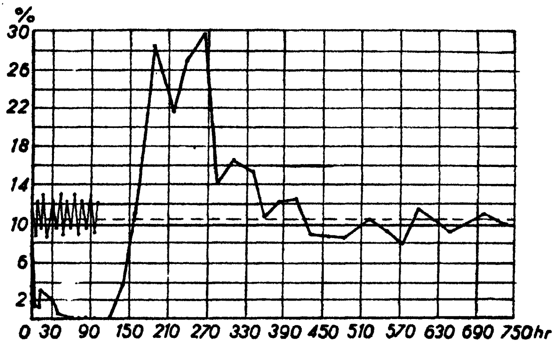


FIG. 33 – Course of the number of mitoses of the spermatogonies in mice-testis after a dose of 300 r. – H. LANGENDORFF, *Strahlentherapie*, Bd. 55 (1936).

2°. A slight resumption of the activity, 3–9 hours.

3°. The occurrence of many, mostly abnormal mitoses, 9–48 hours.

4°. A period of gradual recovery from the consequences of the irradiation during which the mitoses became quite normal again, 2–12 days.

5°. Completely normal pictures, 12–72 days.

Simultaneously, many degenerated cells, gradually cleared away during the recovery-period, were observed in the preparations, especially in the phase lasting 9–48 hours.

ALBERTI and POLITZER (1923) had discovered these diphasic reactions previously in the mitotic activity in preparations of salamander-larvae.

JÜNGLING (1930) observed the diphasic reaction in the mitoses of the roots of *Vicia faba equina*.

In irradiating the testes of mice LANGENDORFF (1936) noticed

that after irradiation with 20 r a retardation of the mitotic activity occurs immediately after the irradiation. 6 hours after, a recovery appears to take place, but now the norm is exceeded and after 40 hours a maximum is reached, after which a slow decline to the normal value follows (Fig. 33).

LANGENDORFF (1936) also discovered a similar reaction in the number of reticulocytes in the blood of white mice after one irradiation with 100, 200, and 400 r respectively (Fig. 34).

With the different kinds of white blood-cells after an initial slight

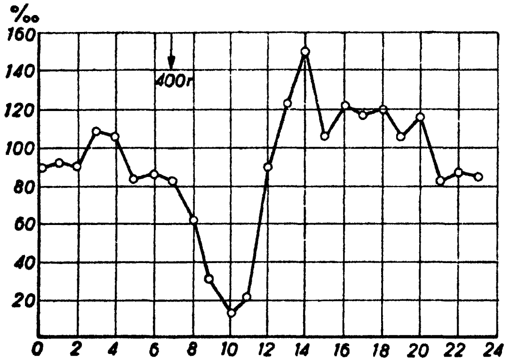


FIG. 34 – Change of the number of reticulocytes of the white mouse after irradiation with 400 r. – H. LANGENDORFF, *Strahlentherapie*, Bd. 55 (1936).

fluctuation during the first hours, a leucopenia exhibits itself after 12 hours. The minimum is reached after 8 days and is followed by a rise beyond the normal to a maximum which then falls slowly to the normal value.

Although most of these observed phenomena are, after all, secondary reactions, they are in each separate case apparently produced chiefly by changes in one particular radio-sensitive substance, which regulates the observed changes. The diphasic nature proves that the reserves do not appreciably diminish during heavier charging. It stands to reason, as was noted before, that there will also be reactions, in which several radio-sensitive substances are simultaneously influenced. In the observed secondary phenomena the different waves are then observed as being superimposed on each other (for example in the erythema of the skin).

The above-mentioned diphasic modifications originated after a

single applied dose. Many experiments also relate to several subsequently administered doses. For the theory, the effect of a continuous irradiation of very long duration would be important, as was carried out in Forssberg's experiments. If the intensity is not too great, then we expect in any case, a decrease to a certain minimum and subsequently a gradual increase to a new steady state at the same or a somewhat different level. In other words, an accommodation to the irradiation must be observable. Now a continuous irradiation covering several weeks is naturally very difficult, so instead we may administer a daily dose which will produce about the same effect, provided it is not too large.

Similar experiments have been made by LANGENDORFF and SAURBORN, (1943) who irradiated two groups of mice with daily doses of 5 r and 20 r respectively. They examined the changes of the spleen, which, as was found previously (POHLE and BUNTING, 1936, among others), to react extremely sensitively.

LANGENDORFF and SAURBORN now found, that 3 hours after the first irradiation nucleus-fragments are present in the lymph-follicles. After the 5th irradiation there is an incipient phagocytosis by cells of the reticulo-endothelial system. The injury still increases and is maximal on the 10th day. Then a gradual recovery sets in, notwithstanding the fact that the daily irradiation is carried on.

After the 30th irradiation there is no difference between the irradiated mice and the controls. The spleen has adapted itself in the way suggested by the theory.

The only difference between the reactions after the daily doses of 5 r and those of 20 r, is that with 20 r the injuries are more serious; the time-course is the same. These phenomena had been observed previously by MOTIDO, KOYEMUNA and SASEO (1937). They thought that the cells examined became X-ray-resistant. LANGENDORFF and SAURBORN, in my opinion, draw the correct conclusions viz. that adaption to the daily irradiation ensues.

The above-mentioned experimental results in which diphasic reactions occur, suggest that in these cases one radioactive substance is chiefly responsible for the observed effects, although they are certainly secondary reactions. In cases where more than one radiosensitive substance is influenced at the same time — and this will mostly occur — the reactions will be more intricate, as we can observe with the erythema of the skin, for instance.

2. Irreversible changes

As was explained in the general introduction to the theory, each biogenic unity consists of a number of groups of homogeneous elements. Each element may be another biogenic unity in itself, but of a lower order. The elements are constantly being constructed and decomposed, during which process construction dominates decomposition for a certain time, which reveals itself as "growth". In course of time, however, a condition comes into being in which construction and decomposition are in a dynamic equilibrium and a quasi-steady state ensues. The biogenic unity is then as a whole constant in the concentration of all groups of elements, if all possible external circumstances are constant. If by varying the external circumstances influences originate which bring about changes in the rate of synthesis and decomposition, then the system of the biogenic unity appears to be stable. Without this property the existence of the biogenic unity would be impossible in a varying environment. Now the last-assumed hypothesis tells us, that, if the number of elements of one of the component groups changes to such an extent, that the relative concentration reaches a certain value, the stable condition passes into an unstable one, so that the balance is disturbed by the least excess and the biogenic unity itself breaks down.

Then such reactions are irreversible. A few simple examples may explain this.

If in man more than one third of the skin is rendered inoperative, death will occur after a short time.

If such changes occur in a cell through some cause or other, so that the osmotic pressure exceeds a certain value (with regard to the environment), then the cell will burst and die.

It makes a great difference of course, what biogenic unity is being examined and what are the elements. For one separate cell death means final extermination. For a whole organ the death of individual cells is of minor importance and, as such, belongs to normal metabolic events, which define the organ as a biogenic unity.

Thus a very weak permanent X-radiation (with the intensity, say, of the cosmic rays) will only produce a temporary change in the elements that compose the skin. All changes are reversible. If the intensity increases, then certain groups of cells e.g., of the matrix or of the blood-vessels, will change irreversibly, i.e. will die. The

fact that the matrix has been partially destroyed or that a number of blood-vessels have disappeared results in the normal reserves of the skin being diminished. The skin as a biogenic unity is still in a stable condition. A new over-straining of these reserves, however, can now easily be caused, so that irreversible changes occur in the skin.

The same holds if we ascend to another stage. The irreversible changes in one portion of the skin do not endanger the life of the individual overlaid with this skin. However, should the destroyed surface become too large, then the whole individual will collapse. If an X-radiation effects such irreversible reactions in a biogenic unity, that the reserves as a whole are permanently diminished without the biogenic unity itself breaking down, we then use the term "conditionally reversible reactions" with regard to this biogenic unity.

3. The limited applicability of the proposed equation of metabolism

From the above it will be clear, that for higher biogenic unities it will be difficult, if not impossible to propose a mathematical formula, which denotes the connection between intensity and irradiation-time, because not only assimilation and dissimilation of a certain organ are influenced by the X-rays, but usually also either directly or indirectly the reserves, both reversibly and irreversibly.

This, in fact, brings us to another problem. Thus far we have been using the following equation of metabolism:

$$\frac{d\xi(t)}{dt} = -I_0 \left\{ 1 + k_1\varphi_1(t) \right\} \xi(t) + L_0 \left\{ 1 + k_2\varphi_2(t) \right\} \varrho(t) \qquad (303)$$

thought to be approximately valid during the irradiation. May we use such an equation to describe the reaction directly on a higher biogenic substance, for instance, on an organ or a tumour, consisting of dividing cells? Of course not, for the equation implies the supposition that assimilation is independent of the number of present elements of X. It may hold if the tissue is formed from a matrix of less-differentiated cells. But if we consider a tumour, it will certainly not hold in this form, because new cells can only be formed from already existing ones. In this case we should use quite another kind of equation.

Let $\eta(t)$ be the number of cells and P_0 and Q_0 the normal dissimilation - and assimilation - coefficients, then we have, before irradiation

$$\frac{d\eta(t)}{dt} = -P_0\eta(t) + Q_0\eta(t) = -(P_0-Q_0)\eta(t) \tag{304}$$

P_0 and Q_0, are not necessarily constants. Moreover, they themselves will now be functions of the milieu and Q_0 especially will be a function of the new matter supplied.

If $P_0 = Q_0$ there will be a steady state, if $Q_0 > P_0$ there will be growth.

During the irradiation there must obtain an equation of the following type

$$\frac{d\eta(t)}{dt} = -[P_0\{1 + \varphi_1(i,t)\} - Q_0\{1 + \varphi_2(i,t)\}]\eta(t) \quad o < t < T \tag{305}$$

and afterwards, for reversible reactions

$$\frac{d\eta(t)}{dt} = -[P_0\{1 + \varphi_1(i,t) - \varphi_1(i,t-T)\} - Q_0\{1 + \varphi_2(i,t) - \varphi_2(i,t-T)\}]\eta(t) \quad t > T \tag{306}$$

The functions $\varphi_1(i,t)$ and $\varphi_2(i,t)$ determine the influence of the irradiation on both coefficients. If one assumes, and for a tissue it seems to be necessary to do so, that direct actions as well as indirect ones influence the life of the separate cells, one cannot make any general statement, about these functions $\varphi_1(i,t)$ and $\varphi_2(i,t)$. One has to accept that the involved nature of the occurrence makes it impossible to find a simple mathematical formulation of every arbitrary reaction. And so, if one relinquishes a similar mathematical formulation for higher biological objects, there will only remain the following:

If $\frac{d\xi(t)}{dt}$ means the velocity with which the number of elements of an arbitrary biogenic substance alters, then

$$\frac{d\xi(t)}{dt} = -\text{diss. velocity} + \text{ass. velocity}$$

Both velocities may be changed by the irradiation. In which direction they will change cannot be predicted, but experience tells us that the dissimilation-velocity is generally increased, directly or indirectly or both. As for the assimilation-velocity one can say that in certain cases it may also be increased either directly by the formation of assimilating ions or indirectly, for instance, by the destruction of certain inhibiting enzymes. On the other hand the assimilation-velocity may be diminished by the fact that the new matter supplied or the alimentary bloodvessels are destroyed. So we can generally say no more, than that all observed (secondary) reactions are the result of a change in both dissimilation – and assimilation – velocity of one or more biogenic substances.

V

THE TIME-FACTOR

1. Schwarzschild's Law

From the preceding chapter it will be clear that SCHWARZSCHILD's law, which says that for a certain effect it^p = constant, can only have the significance of a practical rule, valid within certain limits. As one knows, the exponent p, used as a measure for the time-factor is mostly < 1. There are, however, a number of cases in which $p > 1$ and now difficulties arise how to explain these divergencies from the Bunsen-Roscoe law. In the case where $p < 1$ the generally accepted cause is the power, of a living object to recover from an injury. This recovery-process will start as soon as damaging begins and so it will have its influence on the effect during irradiation and afterwards. But how can it be that by lowering the intensity and increasing the duration this power of recovery may loose its influence although there is more time to develop itself. For this will be the case if $p > 1$. Therefore, one has to find another explanation and it is assumed that it is accounted for by the variations in the radio-sensitiveness of the irradiated cells. The reasoning is as follows: With an irradiation of very short duration only certain cells, being in a very radio-sensitive phase, may be killed. With an irradiation of longer duration there may be more chance that other cells come into that radiosensitive phase and so the effect may be enlarged by diminishing the intensity.

Now I know very well that there are such variations in radio-sensibility. In the mathematical applications of the present theory we have always started, it is true, from stationary conditions, where I_0 and L_0 were supposed to be constants, but we know that very often rhythmical variations around certain mean-values are present. It may be sometimes true, certainly with rapidly dividing objects, that there is such an influence on the effect, so that for very short times there may be an enhancement of the effect by lowering the intensity. In this interval the recovering-potency may be of no importance. By lowering the intensity it must increase its influence, however, and there will be an optimal intensity of minimal strength. When reducing the intensity still more, the recovering-process will

diminish the effect even more. Hence there would be an interval in which Schwarzschild's law approximately holds with $p > 1$, another one in which $p < 1$. Yet I think it doubtful whether the variations in radiosensitiveness may be always responsible for the case $p > 1$. One forgets that when diminishing the intensity and increasing the duration the chance that in every time-unit cells are killed is also decreased and there is no reason to accept that one chance will be better than another.

The truth is that even the conception of recovery is too simple. One only thinks about recovery when there has been damage and one attaches to the organism the property of making good this injury. According to my conceptions *recovery is a consequence of the continuation of the assimilation.* The assimilation does not occur after the injury, it has always been there, although it may be changed by the irradiation itself.

If one now tries to obtain a certain well-defined effect (not a complete reaction) with different intensities, the time-intensity curve or, as one often considers, the dose-intensity curve may have a very intricate structure, especially for higher biogenic substances, as a mere consequence of the mixing up of changes in both dissimilation- and assimilation velocity.

This means, however, that in every interval we may find another exponent p, using SCHWARZSCHILD's law as an approximation, and p may be > 1 as well as < 1, according to the position of the tangent at each point. So it is not necessary to attach two different explanations to the cases $p > 1$ and $p < 1$.

Although it will be impossible to determine generally this dose-intensity curve, it will be valuable to investigate some very simple cases and therefore I may return once more to the equation of metabolism in its most simple form.

Let us suppose that there is one biogenic substance X and let only the dissimilation-velocity be increased proportionally to the intensity. Then

$$\frac{d\xi(t)}{dt} = -(I_0 + c_1 i)\xi(t) + L_0\varrho_0 \qquad (307)$$

In the steady state from which we start $I_0\xi_0 = L_0\varrho_0$ and so, calling again $x(t)$ the relative concentration of X:

$$\frac{d\,x(t)}{dt} = -(I_0 + c_1 i)\,x(t) + I_0 \tag{308}$$

whence

$$x(t) = e^{-(I_0+c_1 i)t} + \frac{I_0}{I_0 + c_1 i}\left\{1 - e^{-(I_0+c_1 i)t}\right\} \tag{309}$$

If a certain effect is reached when $x(t) = 1-A$, then the relation between i and t is as follows

$$\frac{c_1 i}{I_0 + c_1 i}\left\{1 - e^{-(I_0+c_1 i)t}\right\} = A \tag{310}$$

If $it = D$, this will become

$$\frac{c_1}{\frac{I_0}{i} + c_1}\left\{1 - e^{-D\left(\frac{I_0}{i}+c_1\right)}\right\} = A$$

or

$$D = -\frac{1}{\frac{I_0}{i} + c_1}\, lg\left\{1 - \frac{A}{c_1}\left(\frac{I_0}{i} + c_1\right)\right\} \tag{311}$$

If $I_0 = o$ we find that

$$D = \frac{1}{c_1}\, lg\,(1 - A) = \text{constant} \tag{312}$$

which means that the BUNSEN-ROSCOE law will always hold. This is a well-known fact, for in resting-conditions, where metabolism is reduced to a minimum it always obtains and the dose is purely cumulative. If $I_0 \neq o$ but $i = \infty$, we find the same. So the Bunsen-Roscoe law will also hold good for large intensities. For smaller intensities, however, D will increase with decreasing i and we shall have the case $p < 1$, using Schwarzschild's law for not too large an interval. There is, however, an important deviation from this law for very small intensities. Indeed, for

$$1 - \frac{A}{c_1}\left(c_1 + \frac{I_0}{i}\right) = o \text{ or } i = \frac{AI_0}{c_1(1-A)}, \tag{313}$$

D becomes infinite. This means that there is a definite threshold-value for i, below which the effect cannot be reached at all and in

analogy with the same phenomenon which we encountered with electric excitation of the nerve, where we have the Rheobase, I should like to call this minimum intensity the *Radiobase*.

This Radiobase is not restricted to the simplest case discussed. It will also occur if both dissimilation-velocity and assimilation-velocity develop in their own way.

Whether there is a Radiobase in every case, i.e. whether there is a minimal intensity for every irreversible biological irradiation-effect, cannot be predicted of course, but it is of some importance that

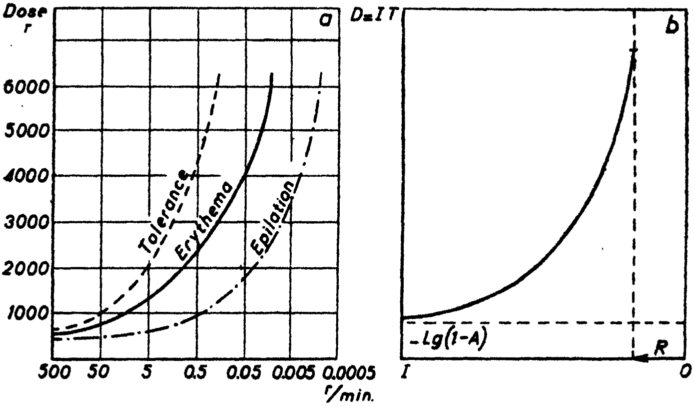


FIG. 35 – *a*. Experimental dose intensity curves according to MUTSCHELLER. – *b*. Theoretical dose-intensity curve for one influenced substance X.

MUTCHELLER, long ago, found such minimal intensities for the skin. Fig. 35a displays a few of these diagrams, while fig. 35b represents a theoretical dose-intensity curve, according to the above-treated example.

In this case there seemed to be no place for an interval, in which for decreasing intensity the total dose should diminish ($p > 1$). It has already been argued that such effects may be expected in secondary and generally more intricate cases. Still I notice that also in the above-treated simple case there must be such an interval if we only consider in which interval the simple equation must certainly fail to be correct. In this equation the enhancement of the dissimilation-coefficient was assumed to be linear with respect to the intensity. This can only be an approximation for not too large in-

tensities and one has to expect that for very high intensities the dissimilation-coefficient will not rise linearly, but will tend to a certain limit. In that case all ions, produced in such a short time, may not all find their partner in the present elements of X. There will be a kind of saturation. Now, if the dissimilation-coefficient rises linearly for ever-increasing i, the Bunsen-Roscoe law would hold. But as this cannot possibly be so, it necessarily follows that the effect must diminish for these very high intensities and according to Schwarzschild's law we must take $p > 1$ in this interval. It is a remarkable fact that SIEVERT and FORSSBERG in 1936 believed that they observed this phenomenon although they themselves are not quite certain that their measurements were sufficiently accurate. When speaking of very high intensities this is, of course, meant in a relative sense. The effect must occur if the number of ions formed is of about the same order as the number of elements of X.

So we can finally conclude that in very simple cases also the dose-intensity curve may be divided into three parts:

1°. For very high intensities (till $i = \infty$) $p > 1$
2°. For medium intensities (approximately) $p = 1$
3°. For small intensities (till i = Radiobase) $p < 1$

It will be clear without more ado that one can treat all kinds of other equations in the same way. But one may see the usefulness of mathematical treatment, even of oversimplified cases, for without this mathematical treatment it would have been very difficult to arrive at the above conclusions.

Finally, I may consider another, also unexplained phenomenon, which has been noticed by REBOUL from the papers of QUIMBY and MACCOMB. When analyzing the results obtained by QUIMBY and MACCOMB with regard to the effects of fractionized irradiation, REBOUL point out the following peculiarity.

A certain effect is obtained after a certain number (n) of daily equal dosages d. So the total dose is D = nd. Now there are given n–1 daily dosages d, but the nth one is applied one or more days later. It appears that this nth dose must generally be larger, according to the length of the interval after which it is given. If, however, this interval is too long (where n = 9, longer than 3 days), this nth dose diminishes again. In other words the total dosage goes through a maximum. REBOUL points out that such an effect is contradictory

to a simple conception of recovery, for the recovery would be less after 3 days than after 4 or 5 days.

This peculiarity can easily be explained if we only assume that both dissimilation- and assimilation-velocity will be increased in their own way by the irradiation. Therefore let us consider again a very simple case in which both these changes occur.

Let a single dose D, given in a short time, be just great enough in order to reduce a certain biogenic substance X to a critical concen-

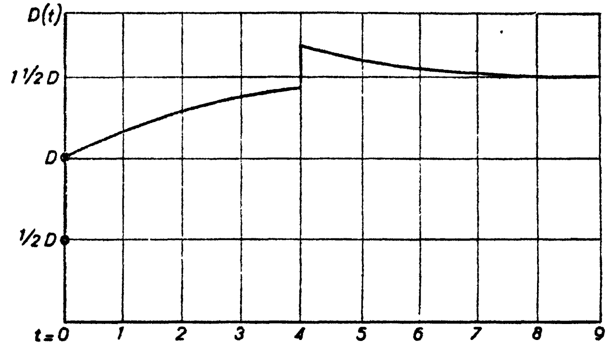


FIG. 36 – A single dosage D may be sufficient to reach a certain effect. If a dosage ½ D is applied at the time t = 0 and a second dosage necessary to cause this effect is supplied at the time t, the curve shows the total dosage D (t). Use is made of the simplified equation

$$\frac{dx(t)}{dt} = - I_0 \left\{ (1 + k_1 i(t) \right\} x(t) + L_0 \left\{ 1 + k_2 i\ (t - \tau) \right\}$$

The effect may be produced if the rel. conc. of one radiosensitive substance reaches a critical value 1 — A.

tration, at which a certain effect will occur. If one gives 1/2 D at once, the effect will not be reached, but a diphasic reaction in the concentration of X will occur. A second dose, given a short time after the first and during the first phase of the reaction must be > 1/2 D in order to reach the required effect, for the assimilation, increasing by the first 1/2 D, will have developed. This second dose must be larger if more time elapses between the first and the second one and it will reach its maximum when it is applied at the moment when the assimilation-velocity has reached its maximum. If, however, we make the interval so long, that the influence of the first 1/2 D has died out, the second dose must be D again and the total dose 1 $^1/_2$ D. So the total dose D(t) will really go through a maximum (Fig. 36).

2. The cumulative dosage

In many studies, authors nowadays are using the conception of a "cumulative dosage". By this the following is meant: If one or more separately applied dosages have been given, which together do not lead to irreversible changes, the effect will disappear gradually. Now, it is supposed that it is possible to define another dosage at every time after the last irradiation which, from that time on, would mean the same for the irradiated object as the actually applied dosages. Moreover, one often assumes that this cumulative dosage should diminish exponentially. According to the conceptions of this theory, such a cumulative dosage cannot exist at all. A singly applied dosage will occasion a series of changes which are exactly determined by the amount of the dose, its qualities and the object upon which it is applied. Part of the reaction cannot be substituted by another smaller dosage.

We must remark, however, that such a conception may have a very practical value within certain limits and as STRANDQUIST has shown, even in clinical problems of therapeutics.

But it should not be used, as is often done, in a theoretical treatment of radiological problems.

It may be superfluous to say that the conception of cumulative dose has a definite sense, when we consider a well-defined irreversible effect. In this sense the conception is never used, however.

VI

RELATIONSHIP TO THE HIT-THEORY

Although the Hit-theory is well-known, the following fundamentals may, however, be recalled.

If we irradiate a large number of homogeneous individuals with a certain dose, then on termination, a certain percentage may exhibit a certain irreversible change in consequence of the irradiation, while the rest lack this change.

Taking a colony of monocellular objects, we can examine what percentage of cells has been killed by the irradiation. The so-called survival-curves represent in some cases an exponentially decreasing function; mostly however, they are sigmoidally diminishing functions of the dose. DESSAUER and BLAU and ALTENBURGER (1923) have, as is well known, tried to explain this by means of the quantum-structure of the X-rays, on the assumption that within the cell there is a certain radio-sensitive volume, which is to be hit by at least a certain number of these quanta. Let N_0 be the original number of cells, a the probability that a "hit" (Crowther) is made by a unit-dose, N the number of survivors and q the dose, it then follows that

$$N = N_0 e^{-aq} \sum_{k=0}^{p-1} \frac{(aq)^k}{k!} \tag{314}$$

in which p is the number of necessary hits.

It was assumed, that the effect occurs independently of the total time within which these p hits occur.

For different values of p different sigmoidal curves are obtained.

We may now try to determine p from the curve and draw further conclusions e.g., about the magnitude of the sensitive volume. There are however some difficulties which indicate that the solution is certainly not exact. This already appears from experiments of CONDON and TERRILL (1938), which provide for their objects a value between 2 and 3 for p.

The solution of this difficulty has been sought in different directions. Thus it has been pointed that individual differences of sensitivity in a large number of individuals, however carefully they may

have been selected, varies. HOLTHUSEN (1927) thought that this individual variability might even be exclusively responsible for the sigmoidal functions.

ZUEPPINGER (1928) especially has tried to give due consideration to this circumstance in the formula. In this study it cannot be further considered. Others, like RAJEWSKI and DÄNZER (1934) and also LEA (1938) have sought a solution from the fact, that the cell may possibly recover from each hit which was inadequate to attain the desired result. We here enter the same domain as is covered by our theory.

They consider the case that one hit does not suffice, but that a second does, provided it occurs within a certain time after the first. In this case they arrive at exactly the same inference, though with another notation. In Lea's notation is

$$N = N_0 e^{-a} \left[1 + at + \sum_{2}^{r_0} \frac{(at)^r}{r!} \left\{ 1-(r-1)\frac{\tau}{t} \right\}^r \right] \tag{315}$$

By τ is meant the interval, within which the second hit should occur after the first. The irradiation-time is t and

$$r_0 - 1 = \frac{t}{\tau}$$

REBOUL (1939) has noted, that in these calculations it was assumed, that, if another hit is achieved *after* the time τ, the disturbance caused by the first must have been quite abolished, in other words, that this second hit may then be looked upon as the first for a following one which, occurring within the new time τ, brings about the effect. This is an assumption, the validity of which, is very questionable. REBOUL has himself proposed a theory which is so important and has so many links with the theory here developed, that I consider a somewhat ampler treatment necessary.

REBOUL points out, that there is an essential difference between the probability that a hit (shock by an electron, quantum, etc.) occurs (probabilité d'atteinte), and the probability that this hit will cause a certain effect, part of the total required effect (probabilité d'action). During the occurrence of several hits until the desired effect is reached, a whole process is going on.

About the first probability nothing is known and only the second can be measured. The latter probability will, in general, depend on the hits already received at different moments, on the reaction of the individual to it, etc. This probability varies, depending on the applied dose.

In general the number of individuals that survive a certain dose, will be

$$N = N_0 e^{-\int a dq} \tag{316}$$

This formula comprises in its generality all other Hit-theories. It admits of some important conclusions. Applying the general formula to experimental survival-curves, we can determine from such a curve the probabilité d'action and determine the variability of this coefficient with the dose. Suppose, we have a sigmoidal survival-curve (Fig. 37), then at each point

$$a = -\frac{\frac{dN}{dq}}{N} \tag{317}$$

We can therefore measure a at each point and we observe that a passes through a maximum for the q for which

$$\frac{\frac{d^2N}{dq^2}}{\frac{dN}{dq}} = \frac{\frac{dq}{q}}{q}, \tag{318}$$

and afterwards tends to a certain limit.

On the assumption, that the different individuals are identical, it follows that there is a change in the radio-sensitivity as a result of the irradiation itself.

In the case where the curve is exponential, this means that the probabilité d'action is constant. Only then is the probabilité d'atteinte equal to the probabilité d'action.

We may now safely say, that this theory perfectly accords with our own conceptions. A single hit may be conceived as a dose administered within negligible time. If this hit effects a change in the relative concentration of the radio-sensitive substance greater than

the critical amplitude, then the matter is forthwith decided and the survival-curve is an exponential one.

If one hit does not suffice, then after this first hit the whole process of changes in dissimilation and assimilation will evolve. Besides the probability that a number of elements of X are decomposed by the first quantum, a new possibility arises, viz. that with the aid of the same quantum or of a few more quanta a number of new elements are being constructed. This new probability may be of a totally different kind. It will depend on entirely different circumstances and on other parts of the cell. As a matter of fact, it

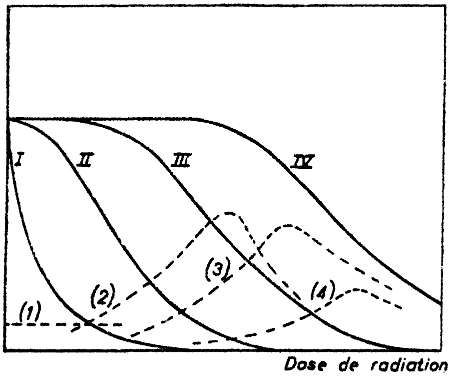


FIG. 37 – I, II, III, IV, Sigmoidal survival-curves. (1), (2), (3), (4), Probabilities. – J. REBOUL in PAUL LAMARQUE: *Les bases physiques et biologiques de la Roentgenthérapie*, Paris 1942.

is quite unnecessary, that the absorbed energy causes only the destruction of certain elements. It can just as well be used for the purpose of building greater elements from smaller ones.

Furthermore, besides the differing probability of decomposition and construction the normal metabolic events superimpose themselves. One single insufficient hit therefore causes changes in sensitivity which can only be neglected after a very long time.

So we arrive at the conclusion that the Hit-theory can only have its value for those cases in which one single ionization in the cell and possibly in a certain very sensible part of the cell causes an irreversible reaction. But also without this argument it may be clear that the supposition that an exactly determined number of hits in or in the neighbourhood of a certain radiosensitive volume

may cause death, is far too simple. A man will be killed by a single bullet going right through the heart. If one fires a salvo from a machine-gun at a mass, a number of persons will be killed. Volleys of different size will kill various numbers and surely sigmoidal survival-curves will originate. But it will not be right to conclude from these sigmoidal curves that all people killed only died by an exactly determined number of shots through the heart. Moreover, it is generally accepted that for tissues, organs and tumours indirect reactions are at least just as important. On the other hand, it is also certain that for isolated cells, mathematical equations, as I used in this study, do not hold good any longer. For these equations imply that we are dealing with continuous or at least quasi-continuous functions. They will only be usable in the form presented if the biogenic substance X which is responsible for the effect consists of a large number of elements. If the effect, for instance, is the occurrence of a special mutation, for which one or perhaps some more ionizations are necessary and sufficient, then the Hit-theory may have its value.

VII

A HYDRAULIC MODEL

It has become customary, we might almost say, to supplement every theory with some analogous model. No great importance can be attached to such a model, but it sometimes helps to visualize the mathematical equations employed. Hence I shall conform to this custom.

Suppose there are a number of receptacles placed above each other viz., R, X and Y (Fig. 38). The bottom of each receptacle contains a number of holes, in which narrow pipes are fixed. The diameters of the several pipes are not equal, but they exhibit variations about a certain average. They are periodically opened and closed by a sliding-lid, which in each bottom moves to and fro with varying frequencies for each bottom.*

A number of pipes in the bottom of R and also of X are shut by a slide I, respectively L. Both slides are coupled to each other.

We now connect R with a reservoir of water E of such dimensions that the level of R will soon be equal to and remain equal to the level in E. As soon as R begins to fill, part of the water will issue through the holes and the level of X will also begin to rise. The drops will reach X only after a certain dropping-time. Subsequently water will begin to flow away from X and a similar thing will happen in receptacle Y. The quantity of water flowing away per second is according to the well-known law of POISEUILLE, proportional to the pressure, i.e., to the amount of water which is present in each receptacle.

In course of time the level in each receptacle reaches a certain height, the amount of water entering from the above-mentioned receptacle being equal to the amount disappearing through the bottom.

If the frequencies with which the pipes are being opened and shut are very high, then practically stationary conditions will ensue. If the frequencies are small, fluctuations around certain levels will originate. The action of X-rays can be demonstrated on this model

* In the figure such a lid which causes rythmical changes (Fig. 33), has only been designed for the upper receptacle R.

by drawing the slides I and L aside for some time and then moving them back to the former position. The first result will be that the level of X will fall and the quantity flowing out diminishes at the same time.

Some time afterwards (on the average τ), the new drops enter which raise the level again and possibly even beyond the normal level, if the slides I and L have been removed to their former position. The variations of the amounts of water in each receptacle with time are in complete accordance with the equations proposed in the theory for reversible changes.

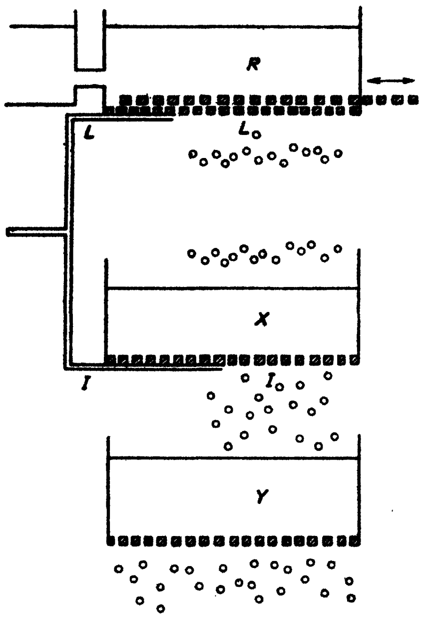


FIG. 38 – Hydraulic model.

VIII

POSSIBILITIES AND LIMITATIONS OF X-RAY THERAPY

1. Problems and technique

The value of a theory is not only determined by the fact that it can explain a large number of phenomena from a small number of hypotheses. The question will always be put, whether it can also present wider perspectives for yet unknown possibilities. If these possibilities can be experimentally confirmed, they will certainly be another support to the theory.

In the case of a theory about the biological action of X- and γ rays, the demand will be in the first place for perspectives for the therapy, especially for the therapy of malignant tumours.

In the course of years, different methods have been gradually developed, which have had a certain measure of success. Yet it cannot be stated, that the results are by any means such, that with the existing methods the ultimate object has been achieved. This may be true for superficial tumours of the skin, but the percentage of cures of the deeper-seated tumours is, in many cases, still small. Of course, this is partially caused by the fact that the patients do not see a doctor or that the diagnosis cannot be made before the tumour has developed considerably. To some extent the difficulty lies hidden in the fact that the treatment is subject to limitations because the deeper-seated tumour has to be reached through the skin and other healthy tissues. In spite of all improvements of the technique of irradiation — various inlets, great skin-focus distance, ultra-high tensities — the tumour cannot be made to disappear in many cases. Sometimes the tumour appreciably reduces, but the treatment has to be stopped, because the skin and the intermediate healthy tissue do not allow further irradiation. In other cases, the tumour will become, as is commonly said, X-ray-resistant and will begin to grow again in spite of further irradiation. The crucial point, as already noted, is that the tumour should be damaged as much as possible and the healthy tissue as little as possible. If the tumour lies at the surface of the skin and if it is very small, matters are fairly simple.

The X-ray tube is placed as near as possible to the tumour (skin-focus-distance 1.8 respectively 1.2 cm in different apparatus for contact-therapy) and, by means of low voltage (50–60 KV) at the X-ray tube, a thinly-penetrating irradiation is chosen. As a matter of fact, this "contact-therapy" nearly always brings about a healing, if only a sufficiently high dose (4,000–10,000 r) is administered. On account of the short distance and the high intensity of the apparatus this high dose can be reached in a few minutes and in the course of about 6 weeks a complete cure is effected.

If the tumour is situated below the surface, very unfavourable conditions arise. Although by increasing the skin-focus-distance and by enhancing the tension at the tube (up to 1 million Volts), the proportions of the amounts of rays absorbed by the healthy and morbid tissues may be lessened, yet the healthy tissue always receives more than the morbid one and a dose once applied within a short time can only be effective, if the tumour is much more radio-sensitive than the irradiated healthy tissue.

The procedure of administering more doses has been used, making use of cross-firing at the tumour from different directions, and also speculating on the various properties of the tumour such as the rate of recovery and possible changes in the radio-sensitivity, which may appear in the course of time and which may be different from those of the healthy tissue. In other words, use is made of the so-called electivity of the tissues.

Now we know the various properties of the skin rather well, but in most cases we know very little of those of the tumour. So, whether the method of simple fractioning according to Stenström and Mattick, the saturation-method of Pfahler, or the method of Coutard with small daily doses and small intensity, is applied or whether the tumour can be approached from different directions or not, in general we proceed thus far, that the skin is strained to nearly the permissible limit.

2. Can the theory be of use in therapy?

We may now ask if the theory here advanced can afford some conclusions or other possibilities for treatment.

The first question that presents itself is: can the theory be applied to a tumour or are we to consider separate cells? I am of opinion

that both possibilities exist, but that it is necessary for the right understanding of X-ray-therapy to view the tumour as a relatively slowly growing biogenic unity in its own environment. With the action on the separate cells as it occurs in the Hit-theory, the complete disappearance of a tumour cannot be understood, for after each part of the treatment cells will be left which have not been killed by the absorbed quanta. The fact that the latter ultimately break down is a result of the activity of the environment, viz. of the reaction of the sound surrounding tissue. For it is generally assumed, that the different adjacent tissues interact upon each other in such a way that under physiological circumstances an equilibrium ensues for both. The growth of the epithelium is retarded by the connective tissue and conversely. With the carcinoma, this balance is disturbed in favour of the pathological epithelium as happens with a more serious injury of the healthy epithelium in favour of the connective tissue, so that scars are caused.

We should, therefore, endeavour by destroying as many tumour-cells as possible to transfer the first equilibrium-disturbance into the second, in other words the concentration of the tumour-cells should have diminished so strongly everywhere, that the surrounding healthy tissue gets the upper hand. There is consequently a critical concentration of the tumour-cells which has to be reached.

A peculiar point of the theory is, that the assumption is made, that the X-rays have not only a destructive action but that they at the same time conduce to a speedier reconstruction, the latter developing as a rule later, which may be called a fortunate circumstance. Finally there is again another circumstance which opposes the quickened growth viz., the alimentary bloodvessels are destroyed. According to the theory, this means that the supply of new matter, from which the tumour has to be built up, decreases and then the possibility of quickened assimilation will diminish again. All this relates to the tumour as a whole.

As regards the separate cells, matters stand as follows: all cells will be damaged sooner or later. Some will collapse because some substance or other diminishes below a critical concentration, either through direct hits or through changes in the humoral environment. With others this does not happen and they will escape death because they can recover in time and the accelerated metabolism — likewise possibly dependent on changes in the environment —

causes a quicker division. These events can be seen microscopically in the well-known diphasic mitotic wave.

3. Some applications of the theory

From the above and also from what has already been said in Chapter IV, it appears that one cannot predict the behaviour under the influence of irradiation from one of the equations of metabolism employed. Only practice can keep us on the right way. But we may ask, whether the theoretical considerations based upon very simple circumstances, can still provide us with new facts and possibilities, which may be of practical use. One has to investigate experimentally whether the conclusions, which "may be" will "really be" for more intricate cases.

Suppose that a continuous irradiation with a certain intensity is employed. There "may be" a minimal intensity, which I have called the *Radiobase* (remember MUTCHELLER's experiments for the skin). The Radiobase, if it exists, is just sufficient to achieve the intended effect. But then, according to theory, it will do so after a very definite time, corresponding with the H.N.Z. of the electrical stimulation of nerve. We may call it the *Maximum Time of Treatment*, for if the effect is not obtained within this time, prolonged irradiation will be ineffective. It is true that for the elaboration of the formulae it was nearly always assumed that the reserves out of which the damaged substance was built up are not diminished by the irradiation. If this does happen all the same, the effect is sooner obtained, which is an advantage, but on the other hand we should take into account that there is damage to the surrounding healthy tissue which constitutes a disadvantage.

With fractionized irradiation the same obtains. Suppose the same dose is administered daily. Here also there may be a minimal daily dose, the *radiobasic daily dose*, which depends of course on the same factors as the Radiobase itself. With this radiobasic daily dose the required amplitude in the concentration of the tumour-cells is just reached. All the above-mentioned conclusions are known or at least presumed from clinical practice.

4. Possibility of a method with creeping-up dosage

But let us see now in what way physiologists investigated the

action of the electric current on the nerve. They reached the intended effect, the excitation, by use of continuous direct current, by condenser-discharges, by separate direct current pulses, by exponentially and linearly increasing currents etc.

If one compares these various methods with the ways in which the radiologist tries to reach his aims, then one sees that he applies his rays exclusively either by continuous irradiation of constant intensity (Radium), or by separated and mostly fairly equal radiation-pulses (fractionized irradiation).

The analogy of the two large groups of phenomena teaches us that it would be valuable to investigate whether other possibilities may have their own use. Particularly it would be of interest to study the effect of exponentially or linearly increasing intensity or daily dosages. The idea of "creeping-up dosages" is not entirely new, but, as far as I know, it has never been studied thoroughly. Let us remember what were the properties of these increasing currents. It has been one of the most remarkable phenomena that excitation failed to appear if the electrical current was made to creep up sufficiently slowly. There existed a "minimal gradient". If the current-strength increases more gradually than is indicated by this minimal gradient, no effect ensues, however great the current-strength may become. This phenomenon was easily explained by the theory here advanced and it serves to show if a similar thing may exist for the behaviour of a cell or a cell-complex. By causing the irradiation to creep up only sufficiently slowly, then great ray-intensities must be reached without irreversible changes being generated.

There may, for instance, exist a minimal gradient for the skin, if with continuous irradiation the intensity is steadily increased. Then, if the intensity increases more slowly, irreversible changes cannot but fail to appear, however great the final intensity might become.

This will of course only be true to a certain extent because this property has been derived from the theory under certain conditions (one definite substance X is affected by the X-rays, $\varrho(t) = \varrho_0$), but for all that we may expect to attain much heavier total doses by sufficiently slow creeping up of the irradiation. A new irradiation-method might therefore be based on this.

Since continuous irradiation with ever-increasing intensity will in practice lead to great difficulties, fractionized irradiation will have to be applied.

We begin with a certain small dose D, for the first day end then ascend every day with a equal amount up to a certain high final value, with which we then continue. It will be necessary first to ascertain experimentally the minimal gradient for the skin. This minimal gradient can be fixed as a minimal first daily dose D_m. It will depend on the intensity, on the quality of the irradiation (tension and filter), of the skin-focus distance and of the portal-dimensions.

We now choose the gradient of the irradiation D_1 somewhat smaller than D_m. It will be necessary of course to examine how far we may really approach a certain maximal daily dose and for how long the irradiation with this maximal dose can be continued.

What was stated about the skin likewise holds for the tumour. The latter may also have its own *minimal* gradient. If the tumour lies deep under the surface, the *actual* gradient of the irradiation for the tumour will be smaller than the one applied for the skin. But by using here also different portals, the unfavourable conditions may improve again. Lastly, whether we shall be successful or not will depend on whether the gradient of the rays absorbed by the tumour is greater than the minimal gradient of the tumour or not.

Perhaps one will object that the skin does not give us the most trouble anymore. By the modern methods of using more than one portal or even by applying rotation-irradiation, one can spare the skin sufficiently. *But what we cannot spare by the common technique, is the immediate environment of the tumour, the tumour-bed.* And this is perhaps one of the most important reasons, why we so often fail. Either the tumour absorbs too few rays, or the tumour-bed is damaged too much. By creeping-up with intensity or with daily dosage in the right way we may spare the tumour-bed, for this one may also have its own minimal gradient.

The whole problem after all resolves itself again into the selectivity of the tissues, by which it is meant that the various tissues possess a complex of properties, differing for each tissue and determining their radio-sensitivity. The smaller the minimal gradient, the greater the radio-sensitivity. That is why $S = \frac{1}{D_m}$ might be a measure of radio-sensitivity.

It is of course a priori by no means certain, that the method of irradiation here proposed will be more effective than the existing

ones, but there is a possibility that it will be; only experiment and practice can decide. A great amount of experimental work will be needed before such a method of irradiation may be applied to patients, but nevertheless I would recommend an examination of the method to those occupied with experimental X-ray biology.

IX

SUMMARY AND CONCLUSIONS

After all the discussions about simple and intricate reactions which are the consequence of irradiation with Roentgen-rays I may finally pass all these in review in order to show clearly, what are the essentials of this theory and to what conclusions it leads.

In the first place, there is the leading principle that with living objects one has to account for the fact that such an object is not a static mechanical system but a dynamic one, in which for all essential parts the eternal *παντα ρει* obtains. By this it is not only meant that there is physical or chemical restlessness. Also in the dead object there is the heat-movement and there may be a number of chemical reactions, which, however, will lead irrevocably to decomposition. There will be an everlasting increase of entropy and from order there will originate disorder. The living object, however, makes order from disorder. It lives on negative entropy, as SCHRÖDINGER says. In the living object there is the mystery of continuous renovation of all essential parts. The ever-lasting decomposition, the dissimilation, is counter-balanced by the continuous rebuilding, the assimilation.

In every living object there is at first a period in which assimilation predominates. Then there comes a relatively long period in which there is a equilibrium between both processes. It is another mystery, as great as Life itself, why this last period, even under very favourite circumstances, more or less suddenly stops and with death dissimilation only remains.

Hence, when we experimentally intervene into a living object by generating ions by some ionizing irradiation, we shall cause a disturbance in this dynamic system. This we call the biological reaction. Perhaps some reader may think that this is quite well understood. Indeed, every-one knows this counteracting of dissimilation and assimilation viz. metabolism and the physiologist can supply you with a large number of particulars, but as soon as the problems and phenomena do not relate to metabolism itself and as

soon as one cannot measure the chemical changes or the absorbed or liberated energy, one makes the living object into a purely physical mechanism, in other words into a dead thing. Unfortunately it appears now and then that the living object behaves in quite another way than would follow from the physical model.

As I remarked before, metabolism is related to Life in its smallest essential particles, where the energy-transformations are not even mesurable. The attaching of an electron to a molecule and the releasing of it are equally matters of metabolism. Indeed, one is a kind of assimilation because the energy of the molecule increases, the other a dissimilation. Moreover, it is of the greatest importance for a molecule, say a protein-molecule in a cell, whether it has been ionized or not. Chemically and biologically it has become quite another thing. But such energy-transformations which may happen continuously, are not measurable. Yet we have known for a very long time that ions play such a part, so that SZENT-GYÖRGYI could say: "I was always led in research by my conviction that the primitive basic functions of living matter are brought about by ions, ions being the only powerful tools which life found in the sea-water where it originated".

Thus it is clear that with our ionizing radiations we may cause such tremendous disturbances in the equilibrium of the living object, for we influence directly the most elementary processes of metabolism and indirectly we also disturb assimilation and dissimilation of higher biogenic substances. It is these changes we observe and between the primary disturbances and those which we observe there is generally a long way. This is responsible for the slow reactions with long latency-times we so often observe in biological objects.

For all biogenic substances it obtains that the velocity with which the number of its elements is altering $\frac{d\xi(t)}{dt}$ is equal to the difference of two other ones, the dissimilation-velocity and the assimilation-velocity i.e.

$$\frac{d\xi(t)}{dt} = -\text{dissimilation velocity} + \text{assimilation velocity}$$

As for the fact that with dissimilation as well with assimilation

ions play a part, we must account for the possibility that both processes are changing, if one exposes the system to ionizing rays. In which direction they change cannot generally be predicted, and especially with higher objects all possibilities may occur, for the changes of both velocities may be secondary reactions as well. From this general principle we can already draw some conclusions. Firstly, one can tell something about the potency of the living object to recover from an injury. According to the simple conception it is a rather mysterious mechanism, which only begins to act as soon as a damaging process has taken place. The general principle, however, teaches us something else. If the ions, formed by the irradiation, have not caused such a disturbance of the dynamic equilibrium that irreversible changes occur, then, after the disappearance of these abnormal ions, both velocities will return to their normal values and the previous state will gradually return. So the potency of recovery is not a special potency of a living object to restore an injury, but a natural disappearance of a disturbance in a dynamic system. A second conclusion is, that a conception like the "cumulative dose" which so often plays a part in theoretical studies, can only have some practical significance. A single, not too strong irradiation will cause a disturbance in the object, which will gradually disappear. The form of this reaction is exactly determined by the applied irradiation and can never be replaced at a later time by another smaller dosage.

Although the reaction of an arbitrary biogenic substance cannot generally be specified, there are, however, a number of cases where things are certainly more evident, which appears from the occurrence of a simple mono- or di-phasic reaction, whereby the metabolism of chiefly one very low biogenic substance has been influenced. With regard to such a primarily-influenced biogenic substance, called X, I assumed some particular hypotheses, which made it possible to formulate the events in metabolism more precisely.

It was assumed that the dissimilation-velocity at every moment is proportional to the number of elements of X itself actually present, while the assimilation-velocity at every moment is proportional to the number of new building-blocks from which the elements of X are to be built up. Secondly, it was assumed that both velocities are proportional to the concentrations of certain activating ions.

Thus if $\xi(t)$ is the concentration of elements of X at the time t and $\varrho(t)$ the concentration of new building-blocks, then, before irradiation starts,

$$\frac{d\xi(t)}{dt} = - I_0\xi(t) + L_0\varrho(t)$$

I_0 and L_0, each proportional to the concentration of certain specific ions, are called the dissimilation- and assimilation-coefficients. If now, by an ionizing radiation, a number of new ions is formed, the rates of both processes may increase. This will not happen at once, however, but just as in chemical processes (compare $H_2 + I_2 \rightleftarrows 2\ HI$), the new velocities will develop only gradually and each in their own way. If we take into account that a decomposition is always easier than a rebuilding, we may presume that the dissimilation will develop much quicker than the assimilation.

The assumption that the assimilation-velocity in such elementary processes may be increased by the irradiation, seems to be insecure, because it is ordinarily supposed that Roentgen-rays only decompose. But I do not see why new-formed ions must necessarily always destroy and why they should not be able to stimulate. Moreover, rebuilding is still a rather complicated process, even with very elementary units and one is free to assume the destruction of a certain inhibiting enzyme as an indirect cause of an enhanced assimilation-velocity. The question is not of much importance. The main thing is, that after an enhanced demolition one often sees an increased rebuilding. This occurs everywhere in nature, not only with elementary processes but also with higher biogenic units. Even in problems concerning economics, where ions do not play a direct part, one sees the same kind of reactions, which may be formally described by the same equations.

Furthermore, it was assumed that the ultimate increase of both ion-concentrations and so of both coefficients, in a first approximation, should be proportional to the intensity, if one irradiates long enough with the same intensity. It was again tried, as in Part II, to describe this gradual increase of both coefficients by the functions of Poisson $\varphi_1(t)$ and $\varphi_2(t)$. After the irradiation, both coefficients return gradually to their original values, if only the disturbance has not led to irreversible changes. In this way we arrive at the following equations:

$$\frac{d\xi(t)}{dt} = -\{I_0 + c_1 i\varphi_1(t)\}\,\xi(t) + \{L_0 + c_2 i\varphi_2(t)\}\,\varrho(t) \quad \ldots\ldots \; o < t < T$$

during the irradiation and afterwards:

$$\frac{d\xi(t)}{dt} = -[I_0 + c_1 i\{\varphi_1(t) - \varphi_1(t-T)\}]\,\xi(t) + [L_0 + c_2 i\{\varphi_2(t) - \varphi_2(t-T)\}]\,\varrho(t) \quad \ldots . \; t > T$$

The Poisson-functions $\varphi_1(t)$ and $\varphi_2(t)$ increase sigmoidally from $o \rightarrow 1$ for $t = o$ to $t = \infty$. The way in which they do so depends on two constants.

Notwithstanding the complicated picture, the above-mentioned equations should be considered simple approximations. One can, however, simplify matters a little more by replacing the gradual development of the coefficients by a discontinuous development. Qualitatively the values of the constants of the Poisson functions are of no importance and so we obtain

$$\frac{d\xi(t)}{dt} = -I(t-\tau_1)\xi(t) + L(t-\tau_2)\varrho(t)$$

In this single equation there occur now two different latency-times, while the interpretation of the equation runs as follows: Before the irradiation both coefficients have their resting-values I_0 and L_0. If irradiation starts, nothing happens during the latency-time τ_1. Then the dissimilation-coefficient jumps from I_0 to $I_0 + c_1 i$, and then returns to I_0 T sec. later. Something similar occurs with the assimilation-coefficient.

Notwithstanding the extreme simplification a number of phenomena can be described very well qualitatively. It appears that all properties of the fungus-cell *Phycomyces Blakesleeanus*, which have been so carefully investigated by A. FORSSBERG, can be predicted by the equation.

Furthermore, the equation shows why the effect of separate dosages is purely cumulative if the object is in a resting state and why the BUNSEN-ROSCOE law does not hold good for small intensities. It can be predicted that there must be a threshold value, called the Radiobase, below which a determined effect cannot occur at all.

From the consideration that the ultimate increase of the coeffi-

cients, which should be proportional to the intensity, cannot hold good for very high intensities, it can even be deduced that for these high intensities the effect must diminish. SIEVERT and FORSSBERG believe they observed this in 1936 and no explanation could be found until now.

Several of the above phenomena are usually described by SCHWARZSCHILD's law. With regard to this law (it^p = constant) the theory generally teaches that it is not necessary to give two separate explanations for the occurring cases $p < 1$ and $p > 1$, as is usual in text-books. The dose-intensity curve must have such a course that in one interval there may be $p < 1$ and $p > 1$ in another one. Furthermore the theory gives rise to serious objections against the Hit-theories, except when the number of necessary hits is one, or at least very small. Finally attention may be drawn to the fact, that although the simple equations cannot be used for higher biogenic substances like tissues and tumours, it may still be expected that some properties are analogous to those of primary reactions. Of course it will be necessary to investigate these things experimentally. Particularly it will be of much interest to know, whether accommodation may occur, at least to a certain extent, if we use creeping-up intensities or daily dosages with a small enough gradient. Should this be true, then there would be a chance that one could show the electivity of the tissues, especially of the tumour and the tumour-bed, to better advantage than with simply fractionized irradiation.

Thus a number of things have once again been reviewed, a multitude of facts, phenomena, explanations and theories, which have been developed over half a century. An attempt has been made to see all these things from a single general principle. More than once authors have thought of such a principle. NEMENOW did, and did not DE BUONO write: "Es scheint dass der biologische Vorgang, worunter wir im allgemeinen die Reaktion der Zelle auf die Bestrahlung verstehen, in der Zelle nicht entstehen kann infolge der einfallenden Energie. Er ist aber die Aenderung eines aktuellen physiologischen Gleichgewichts, das von der in der Zelle befindlichen Energie stammt, die ihr von der elektrischen Atmosphäre, welche die Materie umgibt und ihr Leben verleiht, zugeführt wird. Die biologische Reaktion ist also nach unserer Ansicht kein neu er-

scheinender Vorgang, sondern die Fortsetzung oder Umwandlung eines schon vorher existierenden biologischen Vorgangs".

It has been attempted in this book to give expression to this principle and it has been found in the most general conception of metabolism.

In order to be able to argue and to draw conclusions it was often necessary to make use of mathematical equations. I am sure that in their simplicity and approximation they will often not correspond with reality because of its intricacy. But if they can support our reasoning, so that the reader may accept this principle, when he is thinking about all that is happening to the biological object after irradiation, then they will have fulfilled their task.

EPILOGUE

In this study two big problems have been treated which started from the same biological principle. In view of the fact that this principle is thought to be a quite general one, it may be expected that it can be applied to many other biological problems. Now it is of the greatest interest that recently there have appeared some publications in which the authors have treated their different problems, using the same principle. Of course, it is impossible to give a full and detailed account of these studies but nevertheless it will be of great importance, for my own work also, for the reader to know something of the far-reaching possibilities of the leading principle.

Firstly, there is the monograph of C. N. HINSHELWOOD, F.R.S., *"The Chemical Kinetics of the Bacterial Cell"*, Oxford 1946. This book is a real counter-part to my own. The author, being a chemist, tries to co-ordinate the many chemical reactions which occur in living matter. He chooses the bacterial cell because it is perhaps the most simple complete biological individual. By treating particularly the phenomena of growth, he studies just that problem which I myself tried to avoid as far as possible. Considering the general kinetic aspects of cell-growth, the author supposes the existence of enzyme sequences which are linked together in such a way, that the product of the operation of each enzyme constitutes the substrate for the next one. As cell-growth and division are closely connected with autosynthesis, the differential-equations, by which the chemical kinetics are described differ somewhat from those used in my own study, but the reader will observe the far-reaching analogy with the way of treating the problems as I myself did.

The analogy can be still further extended when we see that much attention is paid to the problem of adaptation and training to drugs and to new sources of carbon and nitrogen. Especially the nature of the lag-phase (relaxation-time, latency-time) is studied, as well as many other problems which are connected with the special problem treated. Finally we find in the chapter of the influence of temperature on the growth-rate of bacteria the same equation:

effective rate of growth = rate of synthesis — rate of degeneration, which in my own study characterizes the biological principle in the most general way.

The second study is of JØRGEN E. THYGESEN of Copenhagen, who wrote an article in the *Acta Radiologica*, Vol. XXVIII (1947), which was entitled: *„On the mechanism of shock or general reaction of cells and organisms to injury"*. This author regards particularly the chemical aspects of cell-injury and the counteraction by special substances. We also find again our hydrodynamical analogy illustrating the successive transformation of substances A, B and C,

$$A \rightarrow B \rightarrow C,$$

in the chemical system of the cell. The author does not use mathematical terms but he considers the stationary state in which *afflux* = *efflux* and regards the reaction of a cell to injury as a disturbance in the dynamical equilibrium of the system. One of his conclusions is: *"The definition of the phenomena of irritation as a reversible disturbance in the steady state of the cell is amplified into a principle of general validity for biological functions"*.

In the third place I would point out the work of my fellow-countryman F. GERRITZEN, M.D., who for many years has studied the rhythmic activity of various organs and especially the disturbance in these organs with patients suffering from diabetes. In a lecture to the Nederlandse Algemene Ziektekundige Vereniging (reported in the *Nederlands Tijdschrift voor Geneeskunde*, 91 (1947) No. 45, the contents of which will also be published in an American medical journal), he points out that one has to regard the human body as a system of organs coupled to each other in such a way, that a constant flow of matter passes from one organ to another. He observes that such streams start from the absorbing organs (intestine, lungs) and, passing through several intermediate organs, are directed towards the excreting organs (lungs, kidneys). In previous articles (*Deutsche Medizinische Wochenschrift*, 21 (1938), and *Acta Medica Scandinavica*, CXI (1942) GERRITZEN communicated experiments which demonstrated that several organs show a rhythmic activity (diuresis, the liver). By using the same hydraulic model he could explain why, for instance, the sugar-

concentration in the blood of healthy persons is constant, notwithstanding the rhythmic activity of the liver and why a rhythm in this concentration appears when there is something wrong with this system, as in diabetes. Most important is that Gerritzen concludes that the idea of a stream passing through a sequence of organs is useful for obtaining an insight into the cause of trouble by studying the variations in the concentration of different substances in the blood. This possibility exists because the blood system is often one of the intermediate organs in the sequence of organs through which a stream of certain substances passes.

These short reports may suffice to show the reader that the principle which formed the base of this study is indeed a general biological one, which can be applied to the events in a single cell as well as to the system of organs in more complicated higher objects, including the human body.

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